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Lillard et al.

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(45) **Date of Patent: *Jan. 12, 2016**

(54) **ANTI-CCL25 AND ANTI-CCR9 ANTIBODIES FOR THE PREVENTION AND TREATMENT OF CANCER AND CANCER CELL MIGRATION**

(75) Inventors: **James W. Lillard**, Smyrna, GA (US); **Shailesh Singh**, Powder Springs, GA (US); **Rajesh Singh**, Atlanta, GA (US)

(73) Assignee: **JYANT TECHNOLOGIES**, Marietta, GA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 159 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/324,633**

(22) Filed: **Dec. 13, 2011**

(65) **Prior Publication Data**

US 2012/0100154 A1 Apr. 26, 2012

Related U.S. Application Data

(63) Continuation-in-part of application No. 13/248,904, filed on Sep. 29, 2011, now Pat. No. 8,512,701, which is a continuation-in-part of application No. 13/233,769, filed on Sep. 15, 2011, now abandoned, which is a continuation-in-part of application No. 12/967,273, filed on Dec. 14, 2010, now Pat. No. 8,097,250, which is a continuation of application No. 10/712,398, filed on Nov. 14, 2003, now Pat. No. 7,919,083.

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(51) **Int. Cl.**

A61K 39/395	(2006.01)
G01N 33/574	(2006.01)
A61K 31/7088	(2006.01)
C07K 16/28	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/7088*** (2013.01); ***C07K 16/2866*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/24* (2013.01); *C07K 2317/76* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Mark Halvorson

(74) *Attorney, Agent, or Firm* — Ping Wang; Andrews Kurth LLP

(57) **ABSTRACT**

Methods for prevention or inhibition of the growth or metastasis of cancer cells in a subject are disclosed. One method comprises the step of administering to the subject a therapeutically effective amount of an antibody to the chemokine CCL25 and/or the chemokine receptor CCR9. Another method comprises the step of administering to the subject a therapeutically effective amount of an expression vector that expresses an antibody to the chemokine CCL25 and/or the chemokine receptor CCR9.

6 Claims, 25 Drawing Sheets

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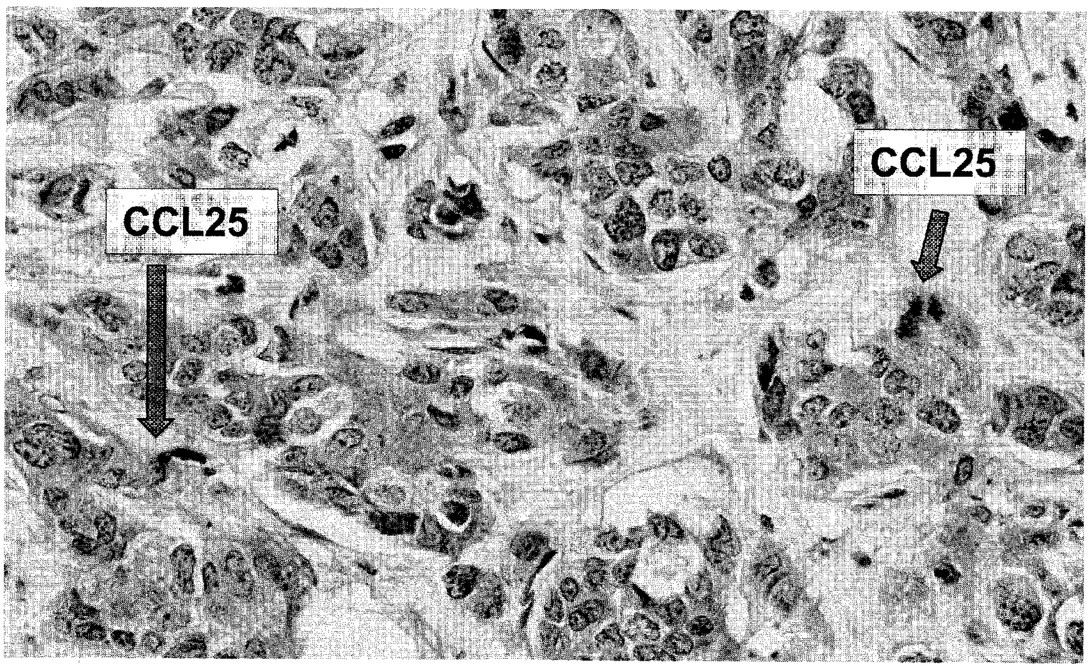
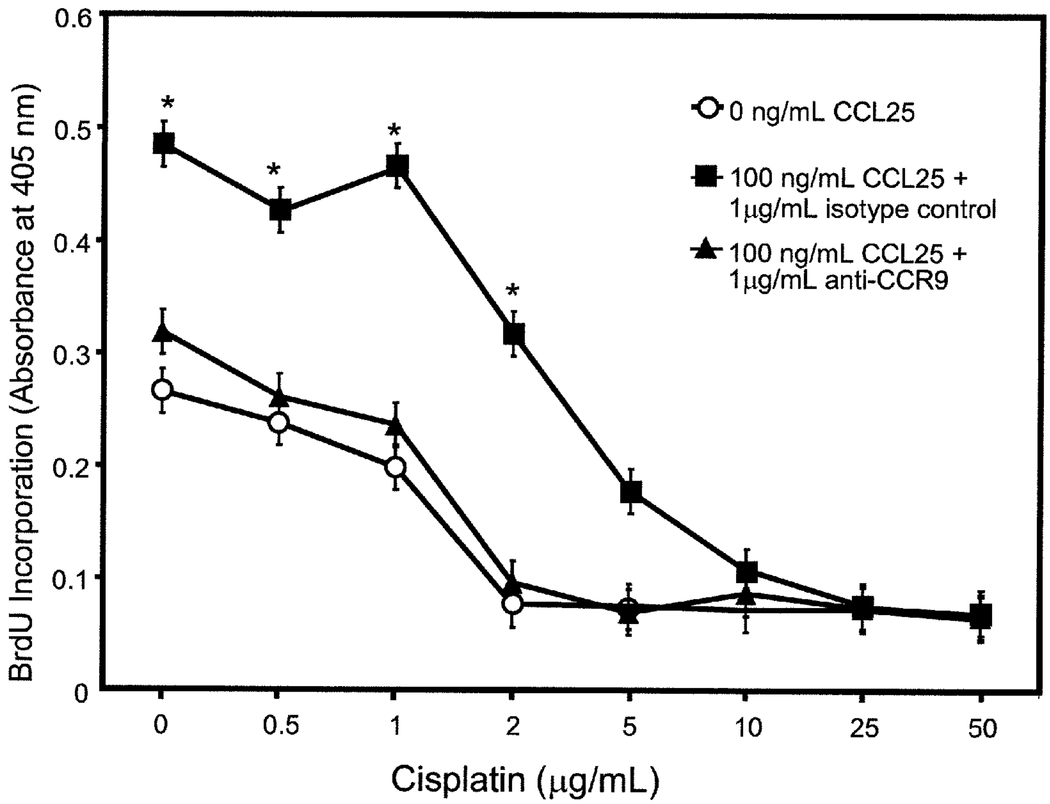


FIG. 1



BrdU Incorporation (Absorbance at 405 nm)
0.6
0.5
0.4
0.3
0.2
0.1
0
0 ng/mL CCL25
100 ng/mL CCL25 + 1μg/mL isotype control
100 ng/mL CCL25 + 1μg/mL anti-CCR9
*
0
0.5
1
2
5
10
25
50
Cisplatin (μg/mL)

FIG. 2

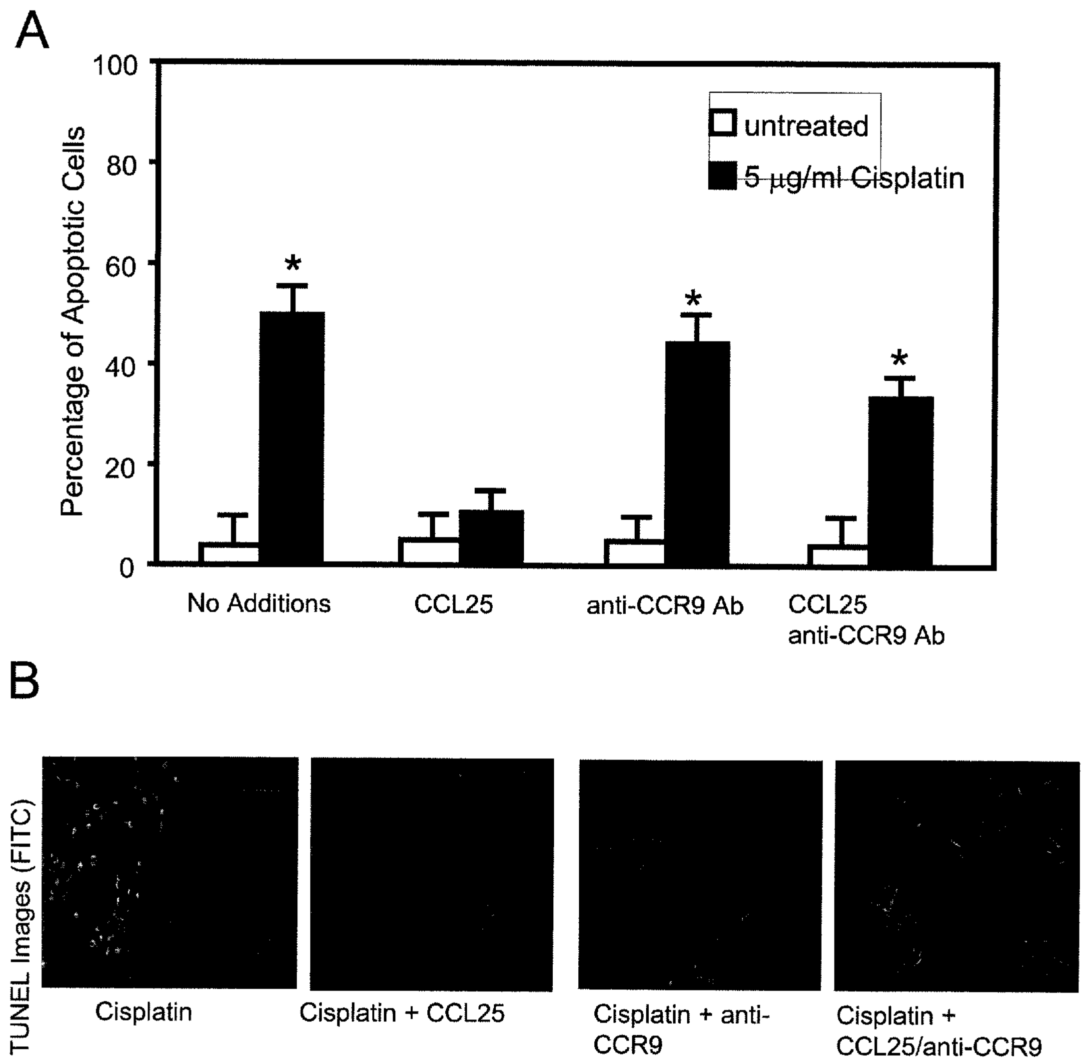

A
100
80
60
40
20
0
Percentage of Apoptotic Cells
untreated
5 μg/ml Cisplatin
*
No Additions
CCL25
anti-CCR9 Ab
CCL25
anti-CCR9 Ab
B
TUNEL Images (FITC)
Cisplatin
Cisplatin + CCL25
Cisplatin + anti-CCR9
Cisplatin + CCL25/anti-CCR9

FIG. 3

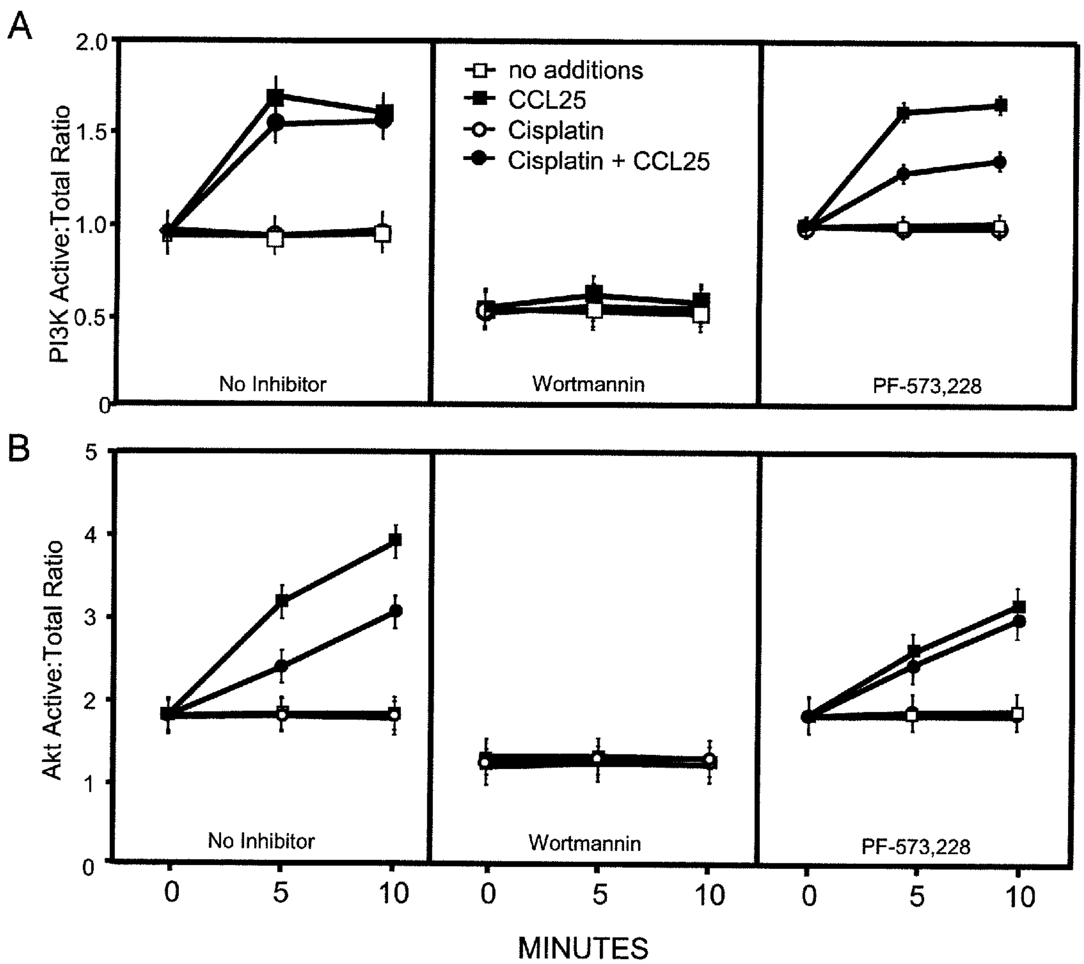

A
2.0
1.5
1.0
0.5
0
PI3K Active:Total Ratio
no additions
CCL25
Cisplatin
Cisplatin + CCL25
No Inhibitor
Wortmannin
PF-573,228
B
5
4
3
2
1
0
Akt Active:Total Ratio
No Inhibitor
Wortmannin
PF-573,228
0
5
10
0
5
10
0
5
10
MINUTES

FIG. 4

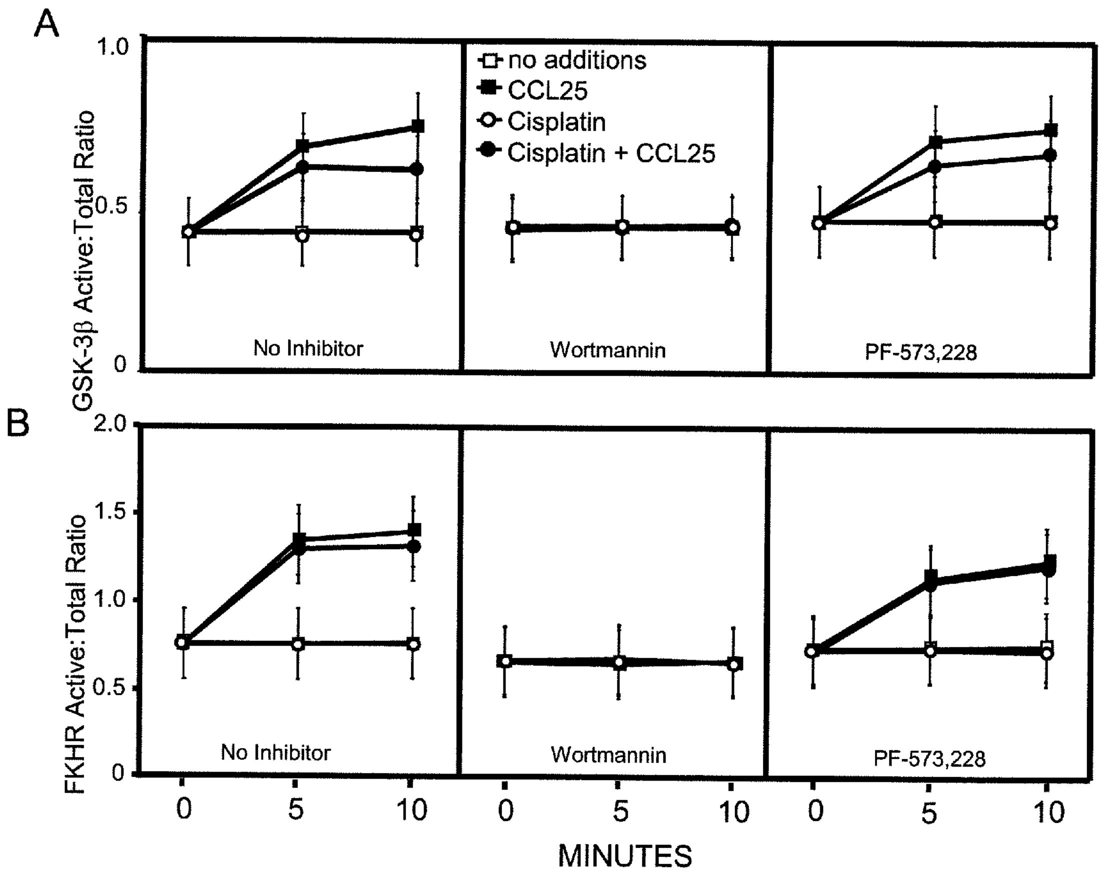

A
B
GSK-3β Active:Total Ratio
FKHR Active:Total Ratio
1.0
0.5
0
2.0
1.5
1.0
0.5
0
no additions
CCL25
Cisplatin
Cisplatin + CCL25
No Inhibitor
Wortmannin
PF-573,228
0
5
10
MINUTES

FIG. 5

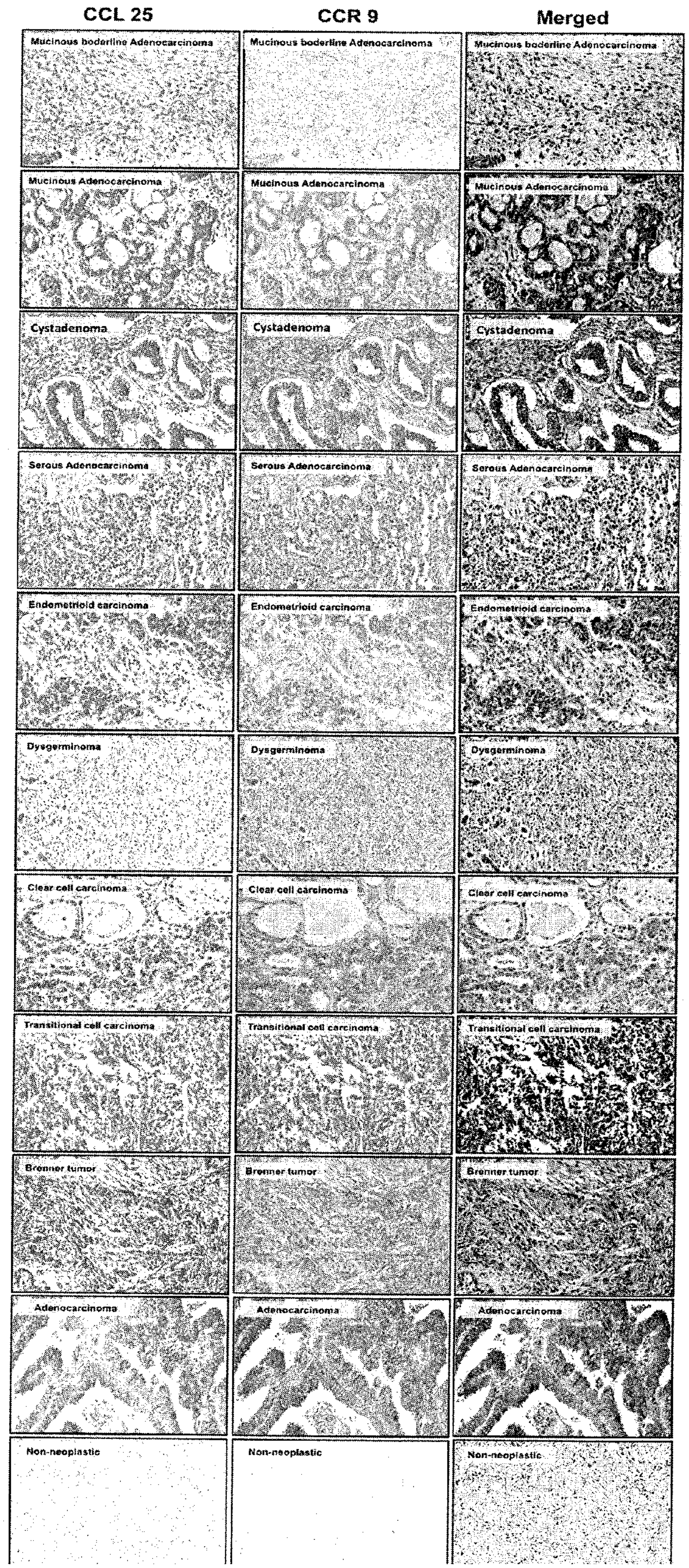
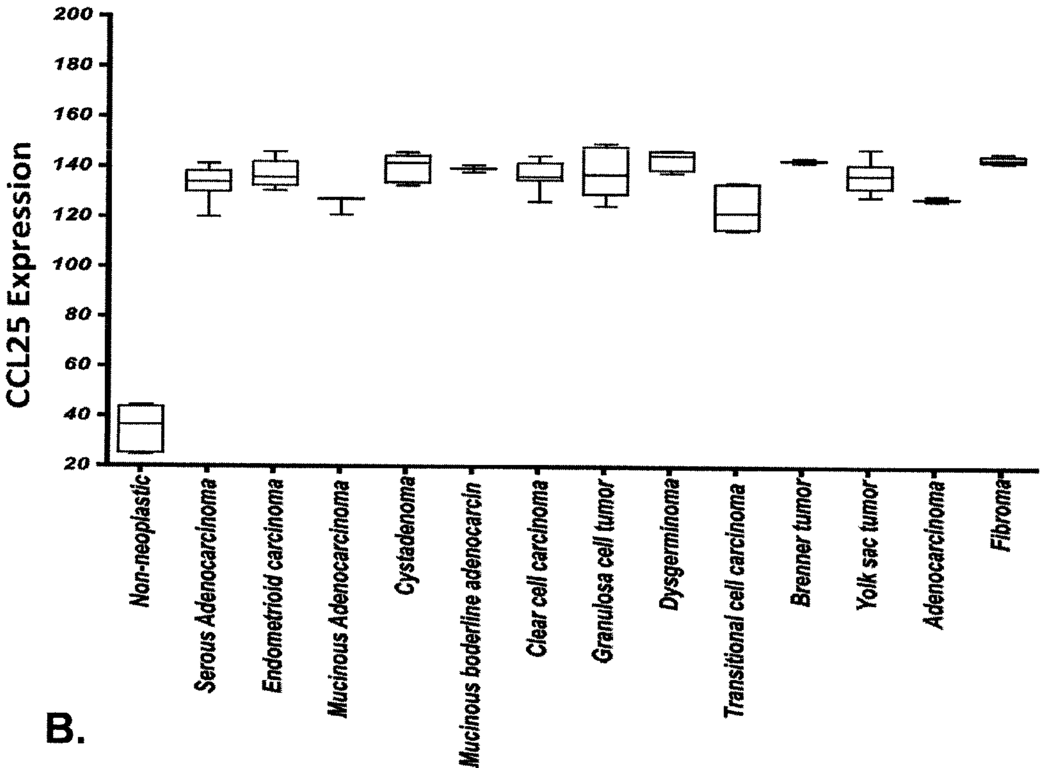

CCL 25
CCR 9
Merged
Mucinous boderline Adenocarcinoma
Mucinous Adenocarcinoma
Cystadenoma
Serous Adenocarcinoma
Endometrioid carcinoma
Dysgerminoma
Clear cell carcinoma
Transitional cell carcinoma
Brenner tumor
Adenocarcinoma
Non-neoplastic

FIG. 6

A.



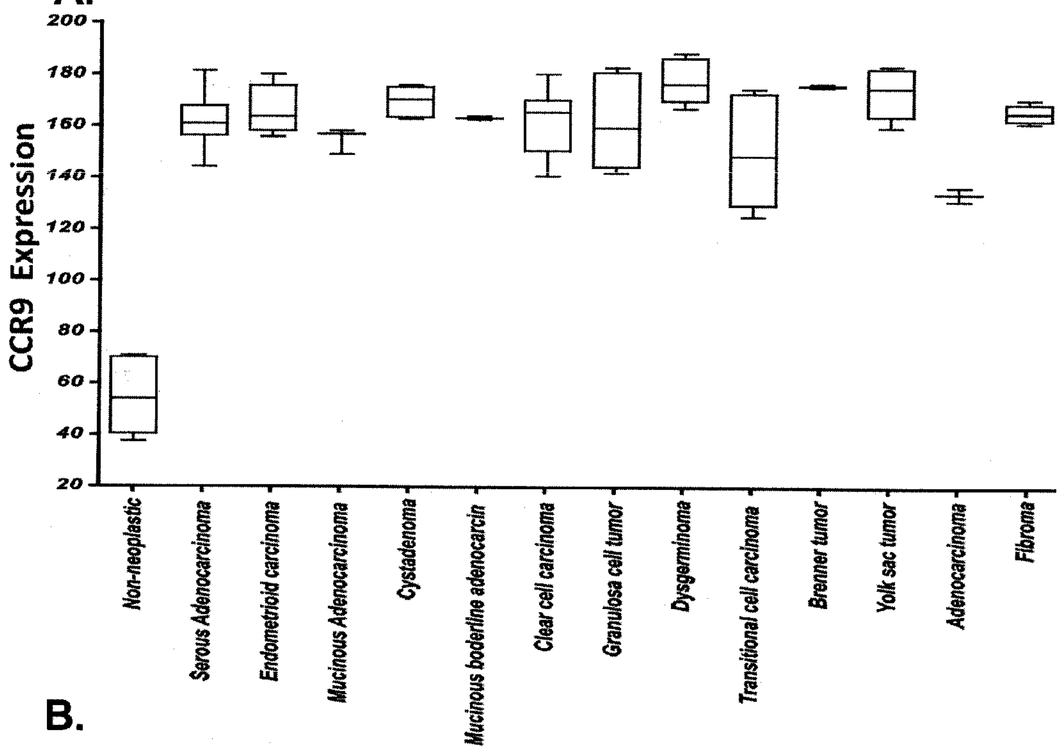
B.

	NN	SA	EC	MA	C	MBA	CCC	GCT	D	TCC	BT	YST	A	F
NN		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
SA			0.1206 (NS)	0.0604 (NS)	0.0283	0.1934 (NS)	0.1006 (NS)	0.1447 (NS)	0.0014	0.0092	0.0519 (NS)	0.1668 (NS)	0.2928 (NS)	0.0044
EC				0.0052	0.3168 (NS)	0.5673 (NS)	0.9844 (NS)	0.7672 (NS)	0.0249	0.0019	0.1727 (NS)	0.9715 (NS)	0.0438	0.0337
MA					0.0031	0.0169	0.0036	0.0531 (NS)	0.0002	0.7556 (NS)	0.0062	0.0162	0.4109 (NS)	0.0003
C						0.8962 (NS)	0.3059 (NS)	0.6892 (NS)	0.2078 (NS)	0.0021	0.4721 (NS)	0.3694 (NS)	0.02	0.1911 (NS)
MBA							0.5619 (NS)	0.8631 (NS)	0.2003 (NS)	0.044	0.1854 (NS)	0.6223 (NS)	0.0235	0.0446
CCC								0.7663 (NS)	0.021	0.0011	0.1609 (NS)	0.9566 (NS)	0.0356	0.0291
GCT									0.2231 (NS)	0.0154	0.5152 (NS)	0.7727 (NS)	0.1797 (NS)	0.2670 (NS)
D										0.0003	0.8634 (NS)	0.049	0.0012	0.8376 (NS)
TCC											0.021	0.005	.5063 (NS)	0.0015
BT												0.2486 (NS)	0.0088	0.5436
YST													0.0922 (NS)	0.0680 (NS)
A														0.0003
F														

NN: Non-neoplastic; **SA:** Serous adenocarcinoma; **EC:** Endometroid carcinoma; **MA:** Mucinous adenocarcinoma; **C:** Cystadenoma; **MBA:** Mucinous boderline adenocarcinoma; **CCC**: Clear cell carcinoma; **GCT:** Granulosa cell tumor;**D:** Dysgerminosa; **TCC:** Transitional cell carcinoma; **BT:** Brenner tumor; **YST**: Yolk sac tumor; **A:** Adenocarcinoma; **F:** Fibroma

FIG. 7

A.



B.

	NN	SA	EC	MA	C	MBA	CCC	GCT	D	TCC	BT	YST	A	F
NN		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
SA			0.2374 (NS)	0.3044 (NS)	0.0823 (NS)	0.8114 (NS)	0.8861 (NS)	0.8564 (NS)	0.0023	0.0998 (NS)	0.0709 (NS)	0.0123	0.0025	0.4221 (NS)
EC				0.0614 (NS)	0.4392 (NS)	0.6438 (NS)	0.3916 (NS)	0.5097 (NS)	0.0251	0.0523 (NS)	0.1758 (NS)	0.1449 (NS)	0.0009	0.9109 (NS)
MA					0.0059	0.1072 (NS)	0.3453 (NS)	0.5383 (NS)	0.0026	0.7341 (NS)	0.0106	0.0136	0.0163	0.0219
C						0.1733 (NS)	0.1739 (NS)	0.3209 (NS)	0.0662 (NS)	0.0451	0.1758 (NS)	0.4252 (NS)	0.0002	0.2741 (NS)
MBA							0.8958 (NS)	0.9127 (NS)	0.0473	0.4205 (NS)	0.0052	0.2012 (NS)	0.0088	0.4415 (NS)
CCC								0.9673 (NS)	0.0139	0.1676 (NS)	0.1485 (NS)	0.0488	0.0115	0.5601 (NS)
GCT									0.0706 (NS)	0.3259 (NS)	0.3205 (NS)	0.1412 (NS)	0.0843 (NS)	0.6662 (NS)
D										0.0104	0.7817 (NS)	0.3961 (NS)	0.0003	0.0242
TCC											0.1330 (NS)	0.0143	0.3117 (NS)	0.1712 (NS)
BT												0.7235 (NS)	0.0042	0.0286
YST													0.0007	0.1794 (NS)
A														0.0008
F														

NN: Non-neoplastic; **SA:** Serous adenocarcinoma; **EC:** Endometroid carcinoma; **MA:** Mucinous adenocarcinoma; **C:** Cystadenoma; **MBA:** Mucinous boderline adenocarcinoma; **CCC:** Clear cell carcinoma; **GCT:** Granulosa cell tumor;**D:** Dysgerminosa; **TCC:** Transitional cell carcinoma; **BT:** Brenner tumor; **YST:** Yolk sac tumor; **A:** Adenocarcinoma; **F:** Fibroma

FIG. 8

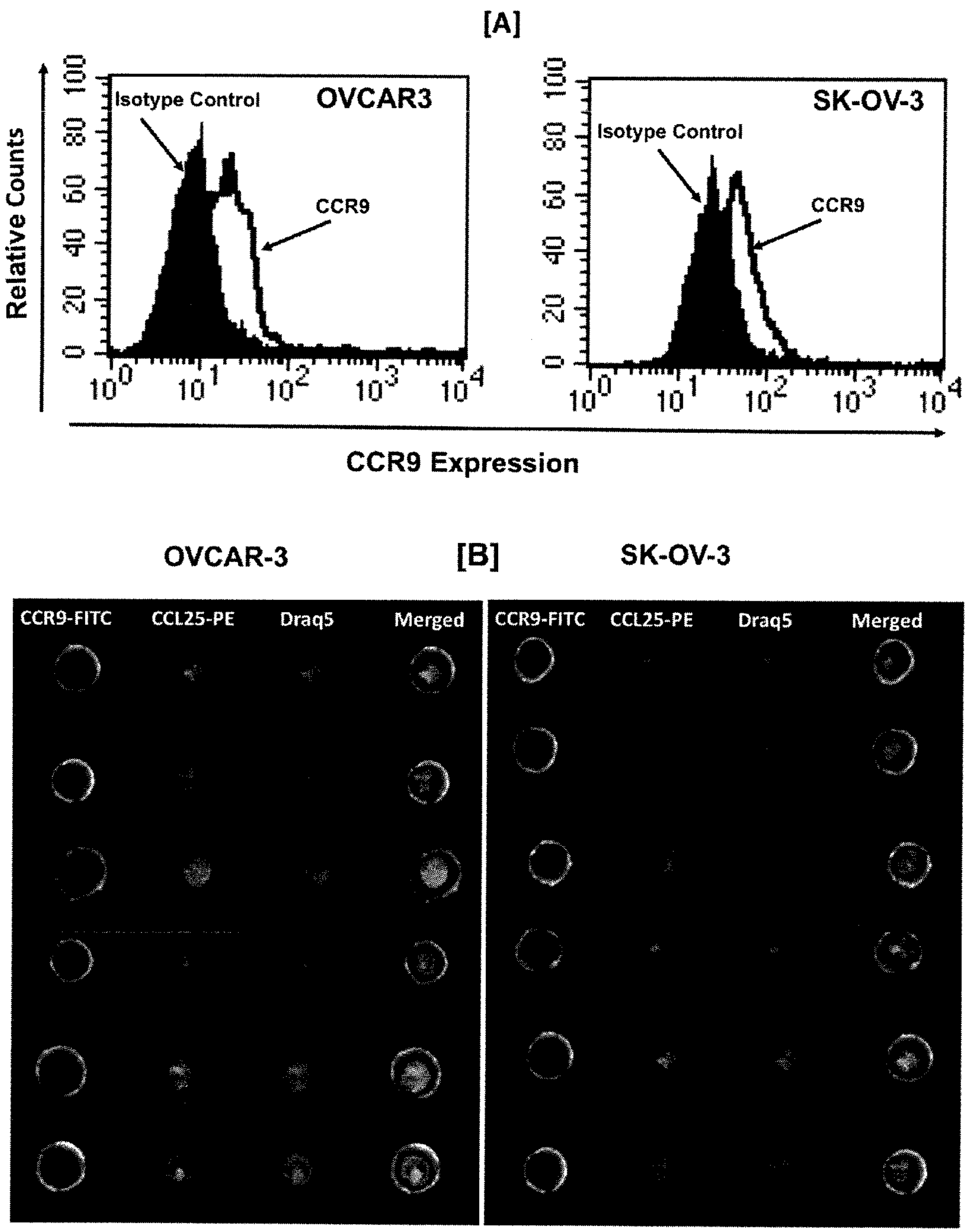

[A]
Relative Counts
Isotype Control
OVCAR3
CCR9
Isotype Control
SK-OV-3
CCR9
CCR9 Expression
OVCAR-3
[B]
SK-OV-3
CCR9-FITC
CCL25-PE
Draq5
Merged
CCR9-FITC
CCL25-PE
Draq5
Merged

FIG. 9

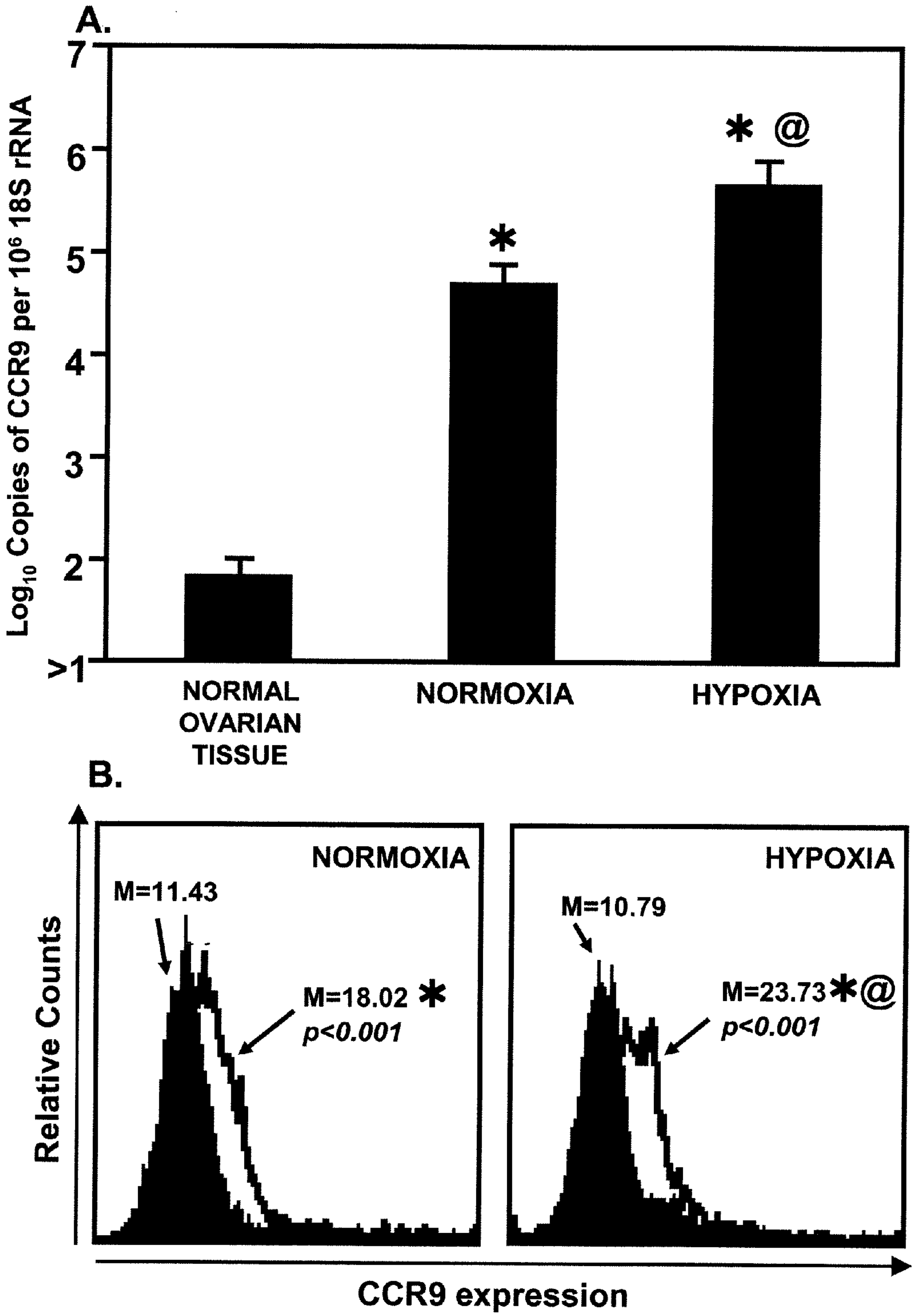
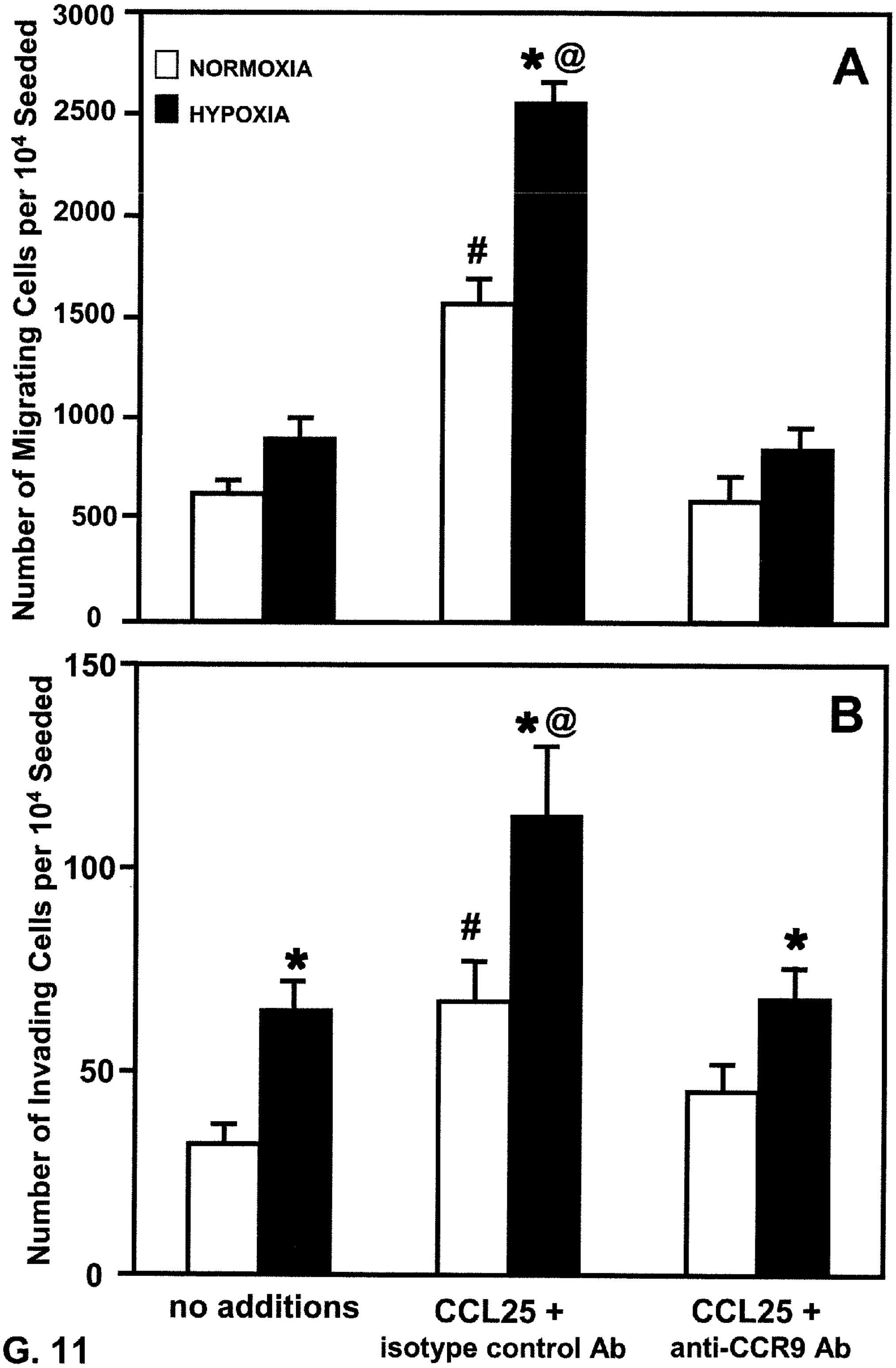

A.
7
6
5
4
3
2
>1
Log10 Copies of CCR9 per 10^6 18S rRNA
*
* @
NORMAL OVARIAN TISSUE
NORMOXIA
HYPOXIA
B.
NORMOXIA
M=11.43
M=18.02 *
p<0.001
HYPOXIA
M=10.79
M=23.73*@
p<0.001
Relative Counts
CCR9 expression

FIG. 10



Number of Migrating Cells per 10⁴ Seeded
3000
2500
2000
1500
1000
500
0
NORMOXIA
HYPOXIA
A
*@
#
Number of Invading Cells per 10⁴ Seeded
150
100
50
0
B
*@
#
*
*
no additions
CCL25 +
isotype control Ab
CCL25 +
anti-CCR9 Ab

FIG. 11

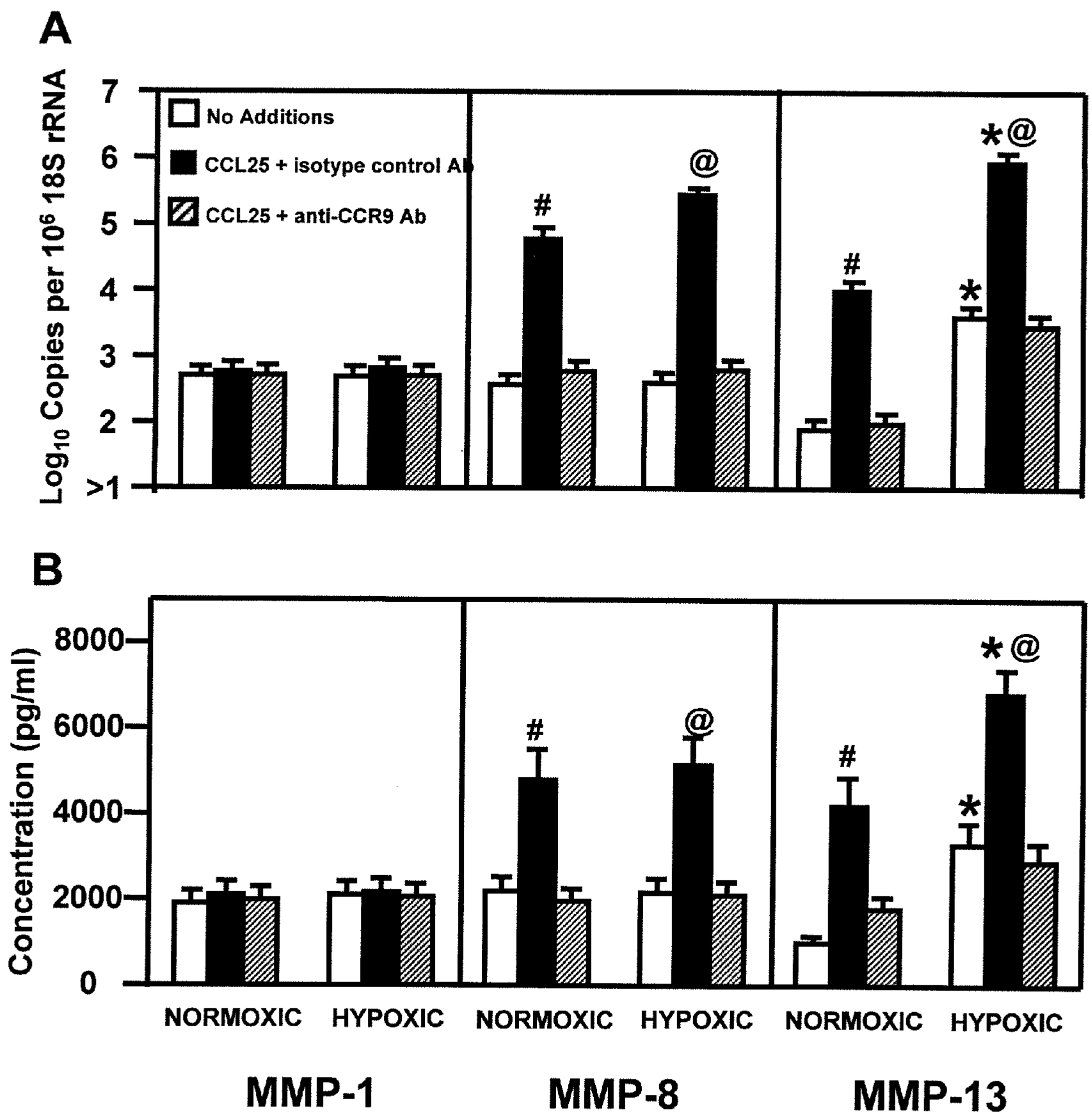

A
Log10 Copies per 10^6 18S rRNA
7
6
5
4
3
2
>1
No Additions
CCL25 + isotype control Ab
CCL25 + anti-CCR9 Ab
#
@
#
*@
*
B
Concentration (pg/ml)
8000
6000
4000
2000
0
#
@
#
*@
*
NORMOXIC
HYPOXIC
NORMOXIC
HYPOXIC
NORMOXIC
HYPOXIC
MMP-1
MMP-8
MMP-13

FIG. 12

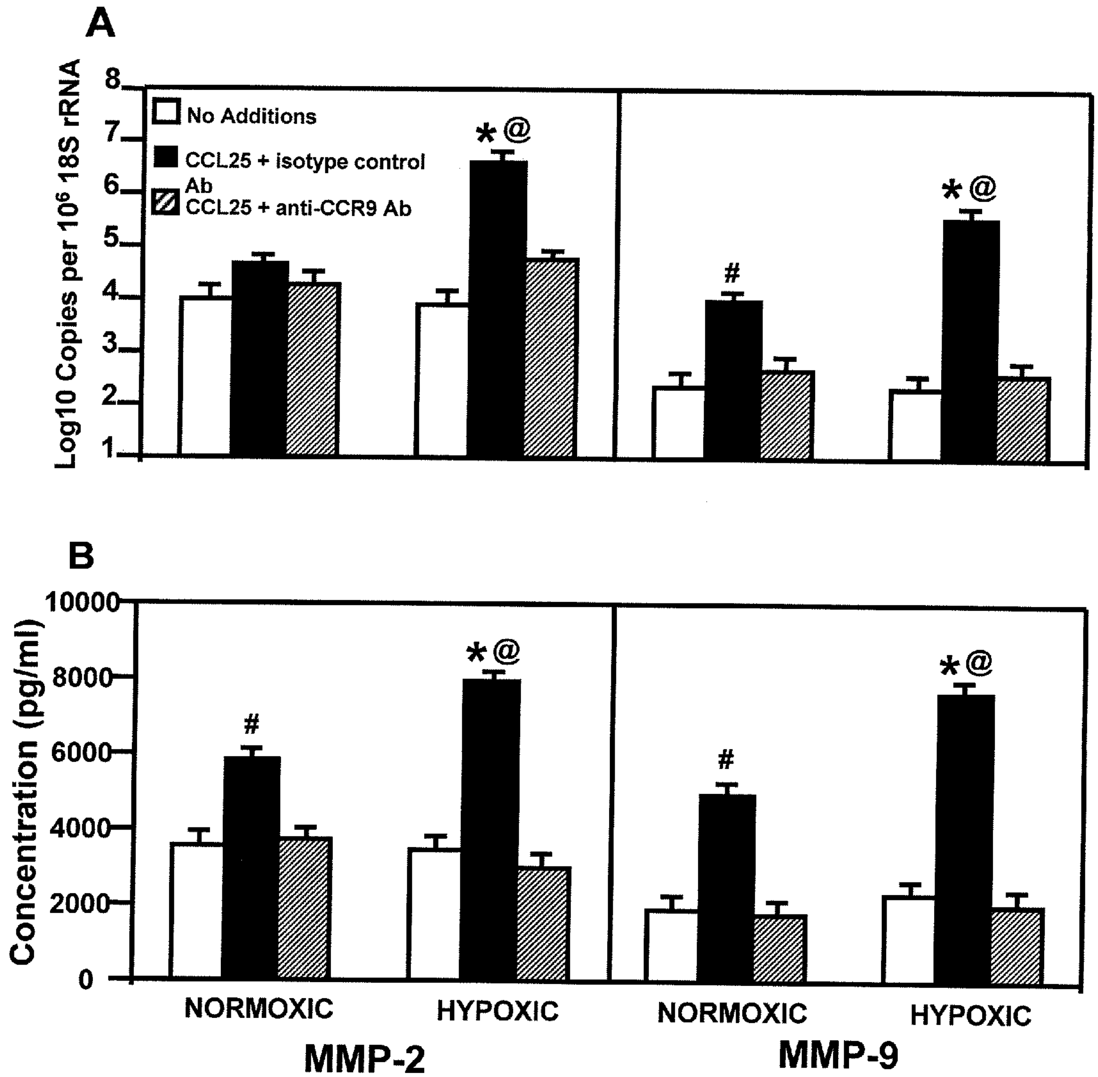

A
Log10 Copies per 10^6 18S rRNA
8
7
6
5
4
3
2
1
No Additions
CCL25 + isotype control Ab
CCL25 + anti-CCR9 Ab
*@
#
*@
B
Concentration (pg/ml)
10000
8000
6000
4000
2000
0
#
*@
#
*@
NORMOXIC
HYPOXIC
NORMOXIC
HYPOXIC
MMP-2
MMP-9

FIG. 13

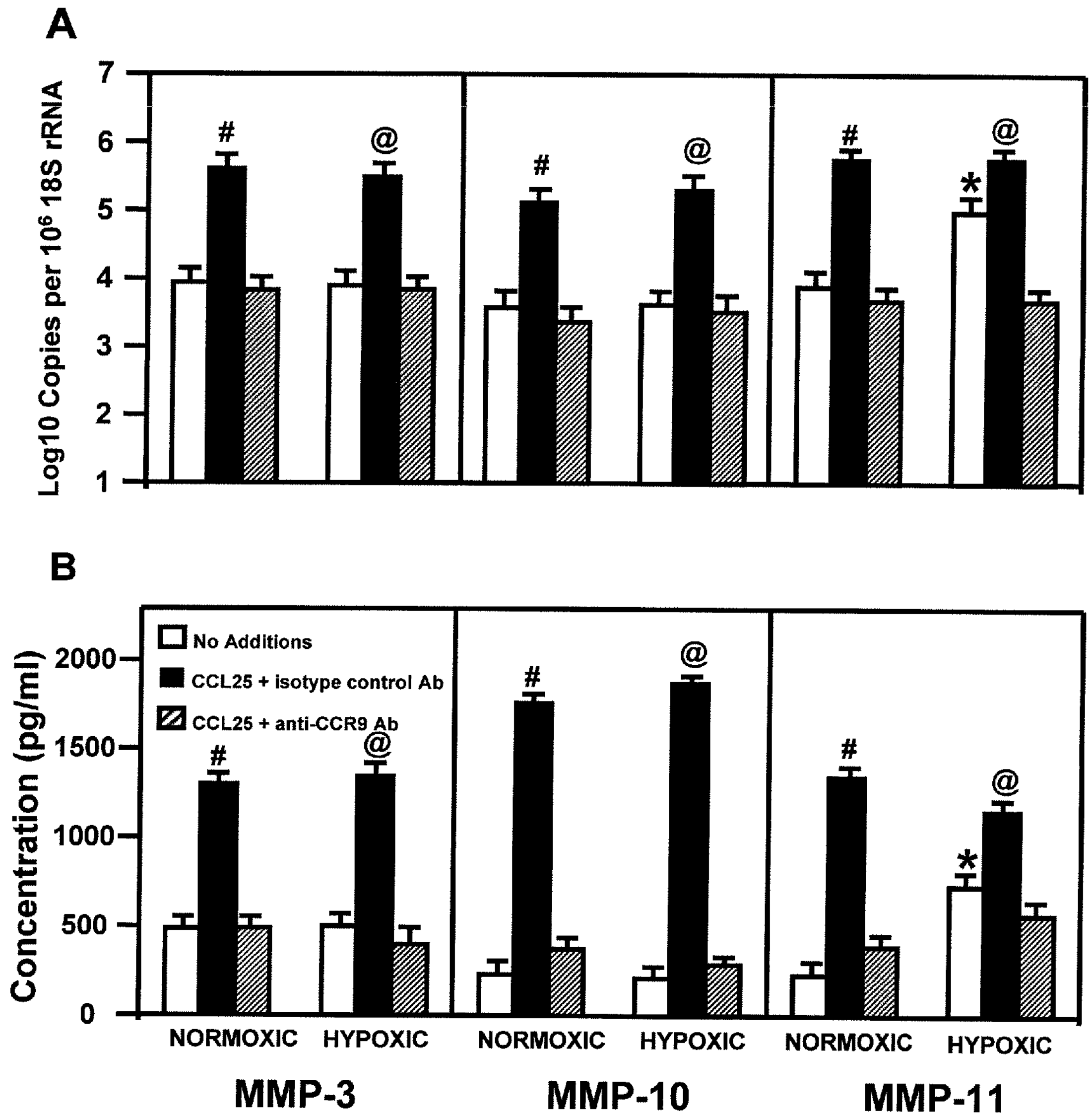

A
Log10 Copies per 10^6 18S rRNA
7
6
5
4
3
2
1
#
@
*
B
Concentration (pg/ml)
2000
1500
1000
500
0
No Additions
CCL25 + isotype control Ab
CCL25 + anti-CCR9 Ab
NORMOXIC
HYPOXIC
MMP-3
MMP-10
MMP-11

FIG. 14

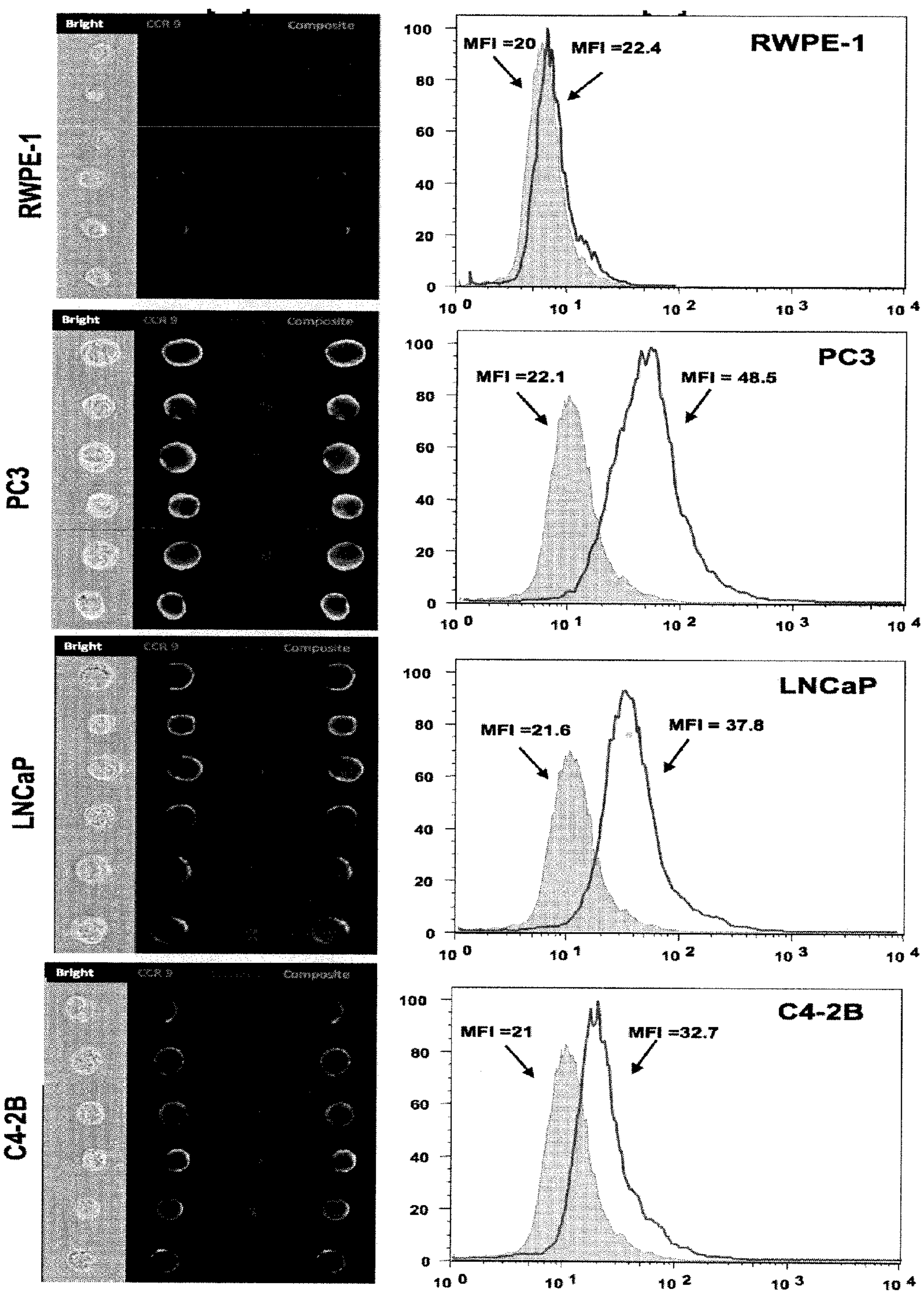

RWPE-1
Bright
MFI =20
MFI =22.4
RWPE-1
PC3
Bright
MFI =22.1
MFI = 48.5
PC3
LNCaP
Bright
MFI =21.6
MFI = 37.8
LNCaP
C4-2B
Bright
MFI =21
MFI =32.7
C4-2B

FIG. 15

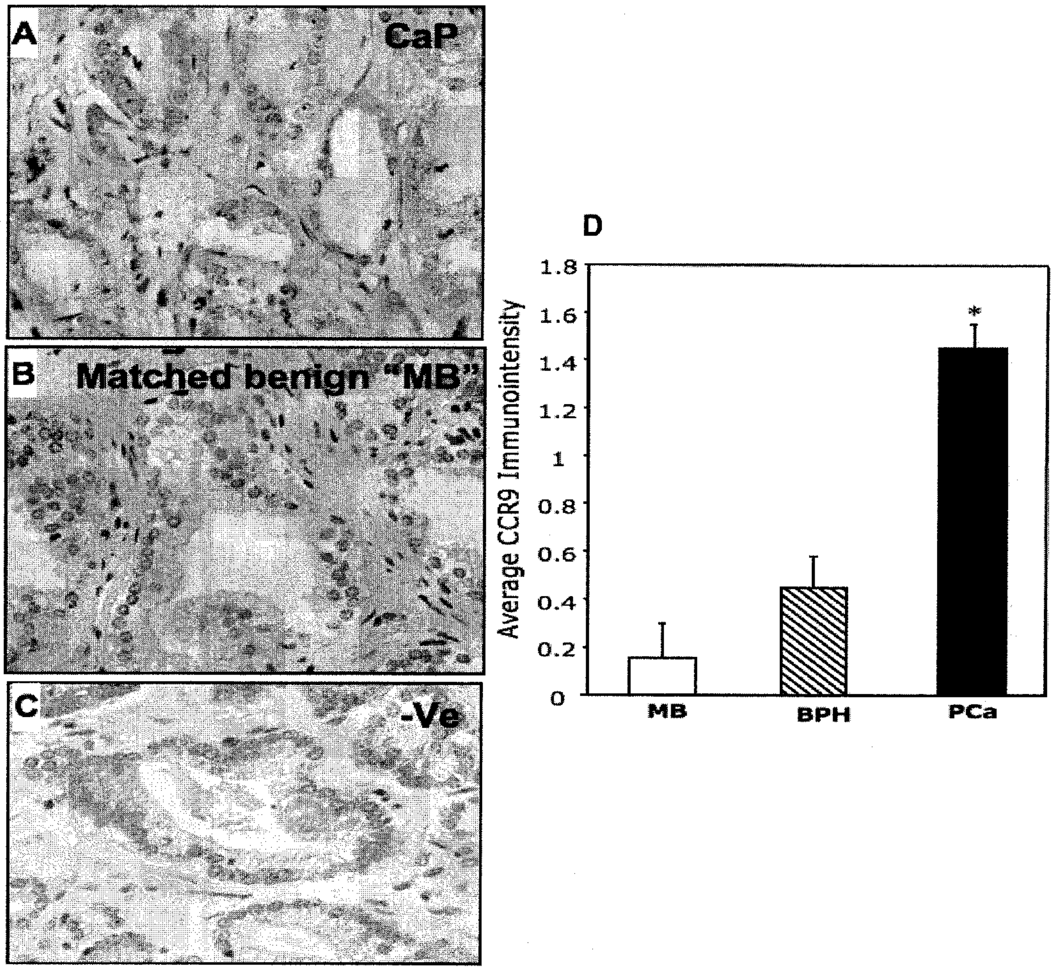

A
CaP
B
Matched benign "MB"
C
-Ve
D
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Average CCR9 Immunointensity
*
MB
BPH
PCa

FIG. 16

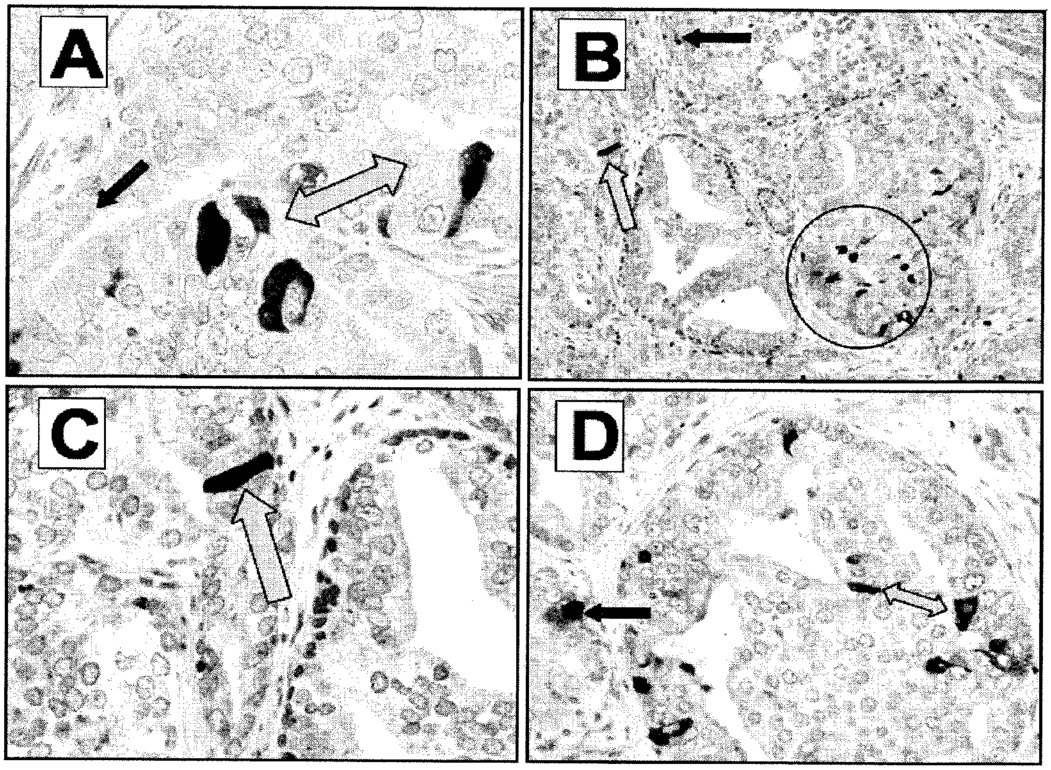


FIG. 17

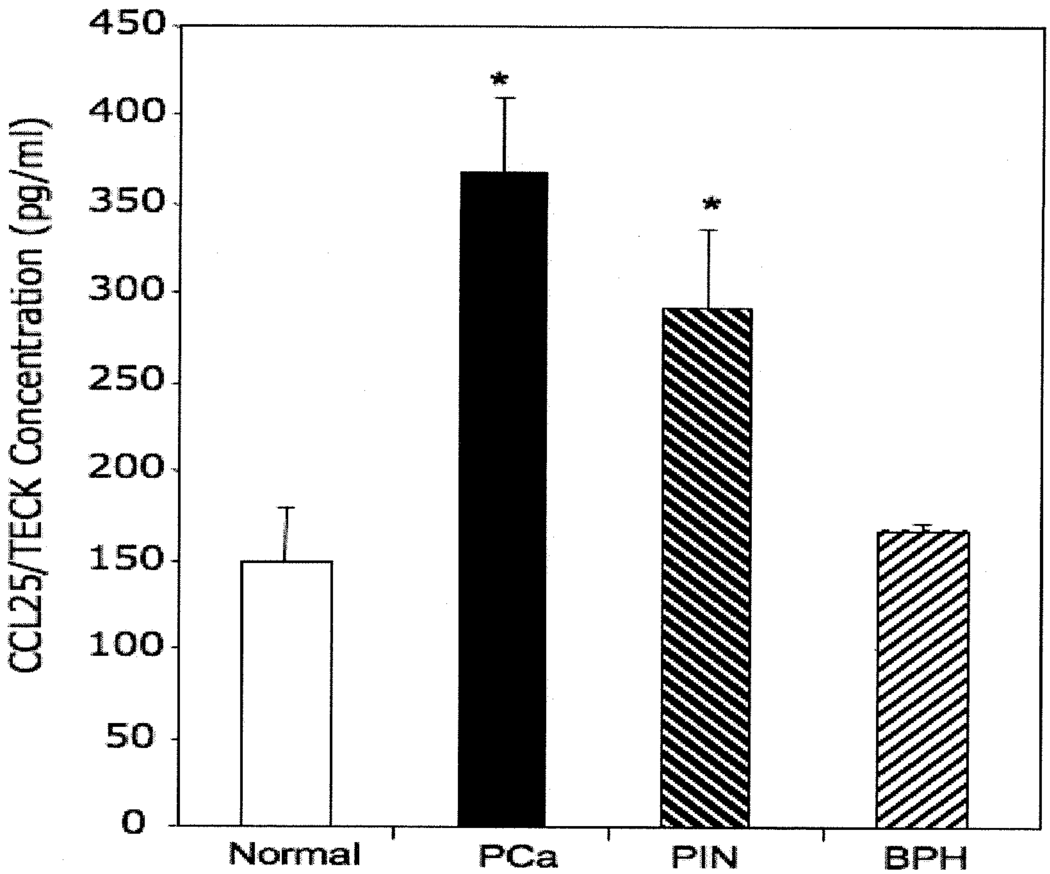

CCL25/TECK Concentration (pg/ml)
450
400
350
300
250
200
150
100
50
0
*
*
Normal
PCa
PIN
BPH

FIG. 18

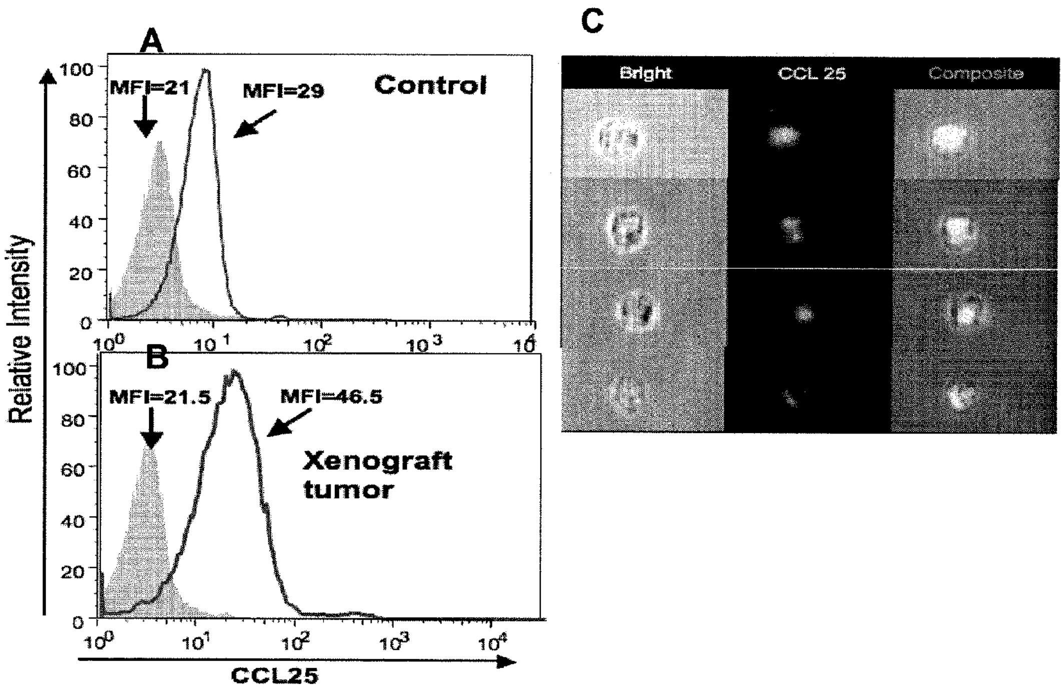

A
MFI=21
MFI=29
Control
B
MFI=21.5
MFI=46.5
Xenograft tumor
Relative Intensity
CCL25
C
Bright
CCL 25
Composite

FIG. 19

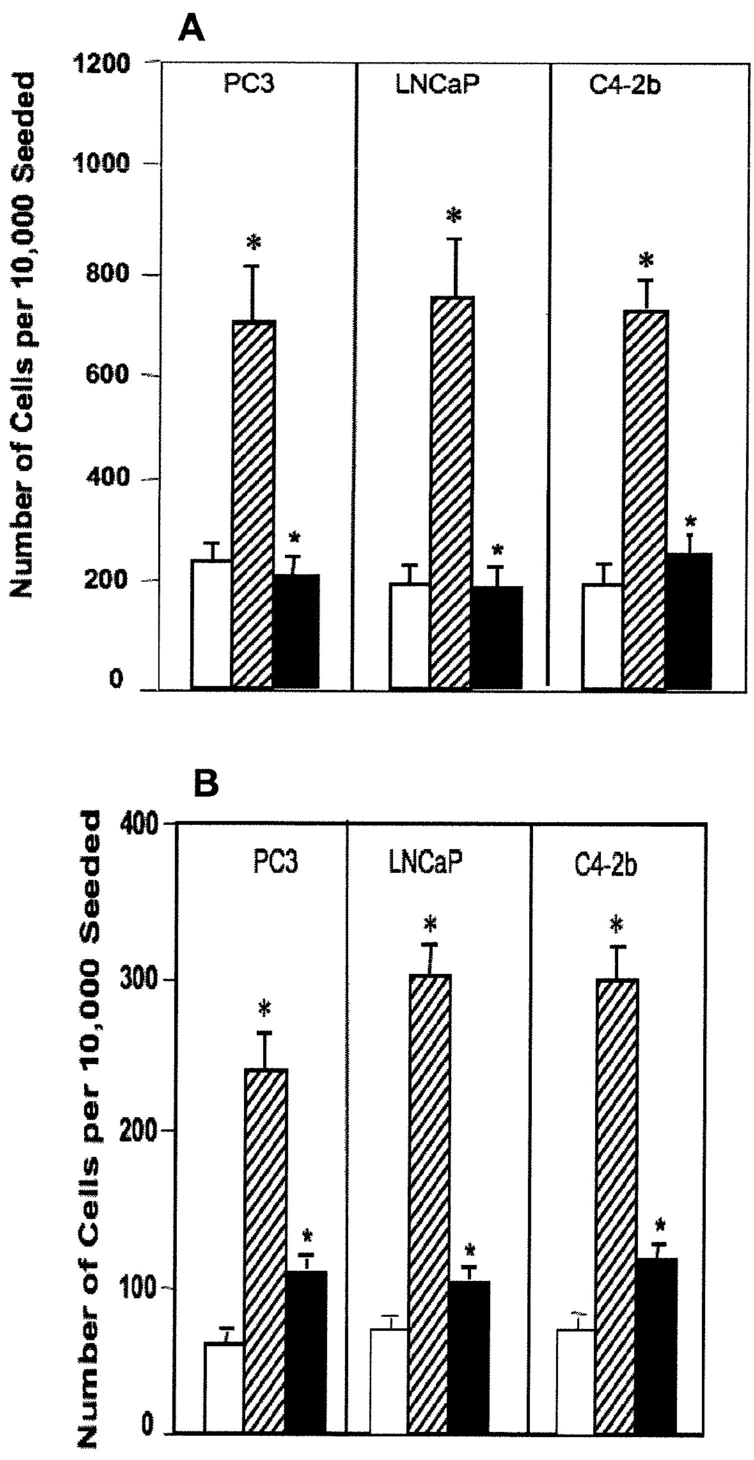

A
1200
1000
800
600
400
200
0
Number of Cells per 10,000 Seeded
PC3
LNCaP
C4-2b
*
*
*
*
*
*
B
400
300
200
100
0
Number of Cells per 10,000 Seeded
PC3
LNCaP
C4-2b
*
*
*
*
*
*

FIG. 20

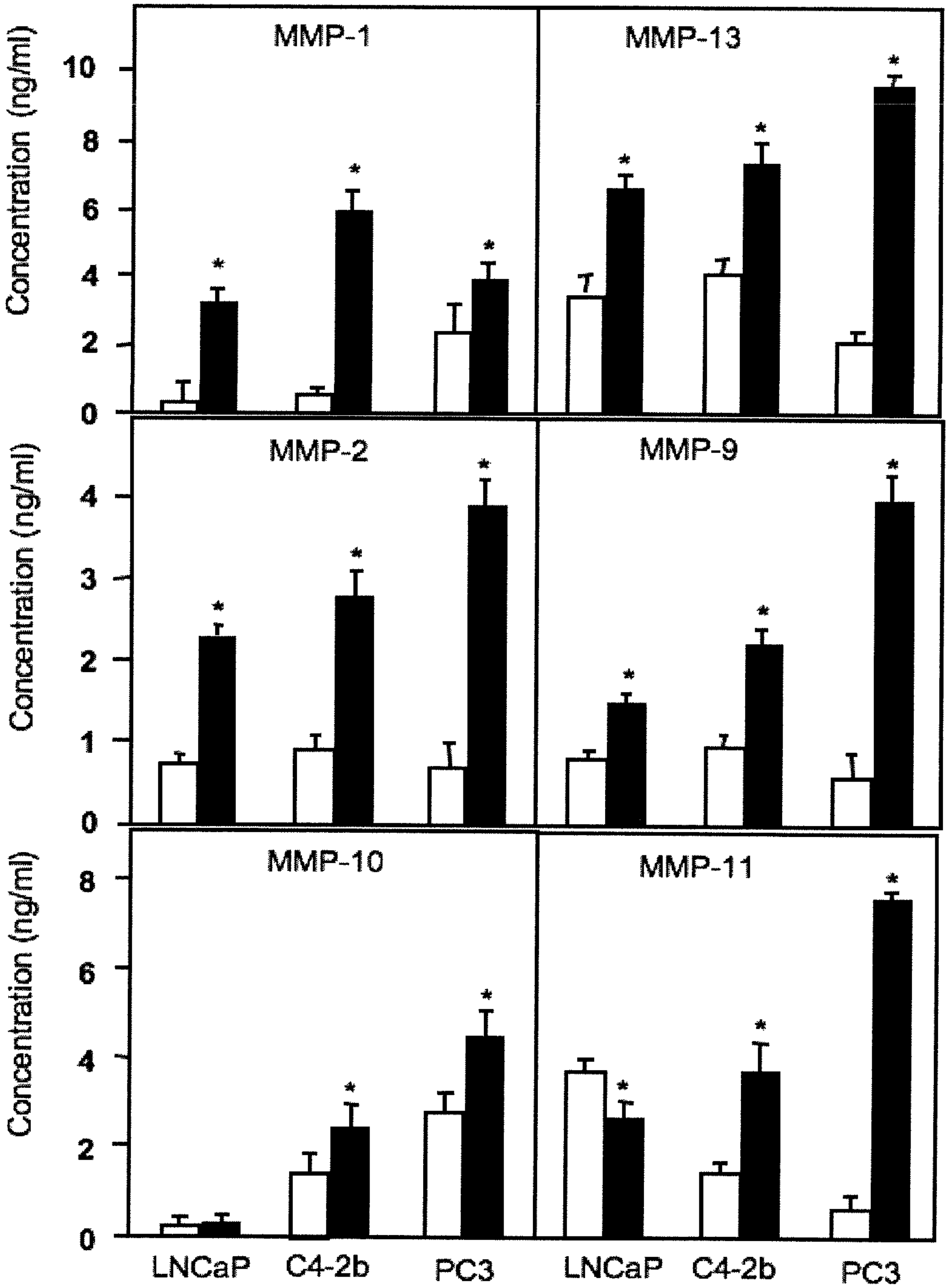

MMP-1
MMP-13
MMP-2
MMP-9
MMP-10
MMP-11
Concentration (ng/ml)
LNCaP
C4-2b
PC3

FIG. 21

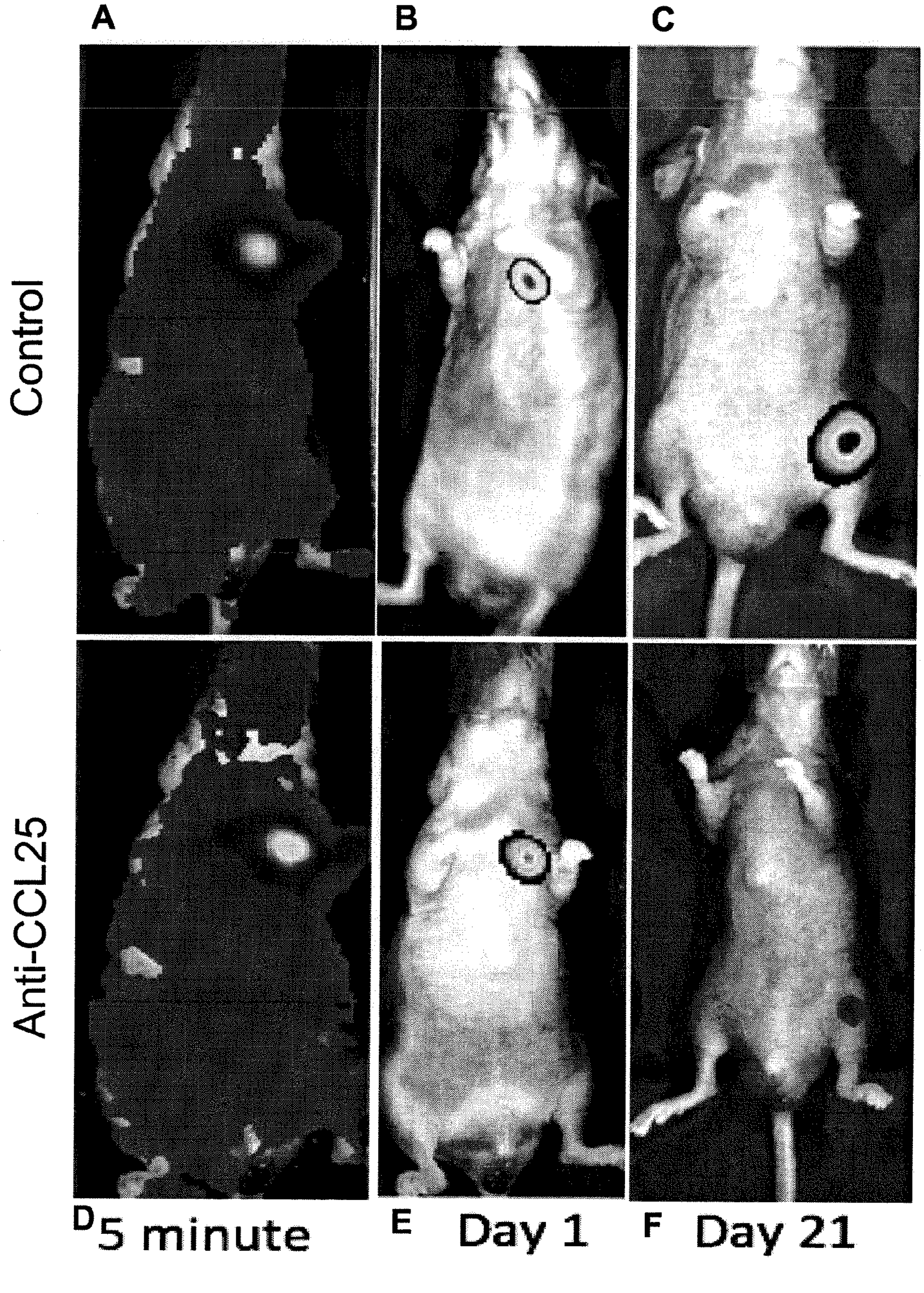
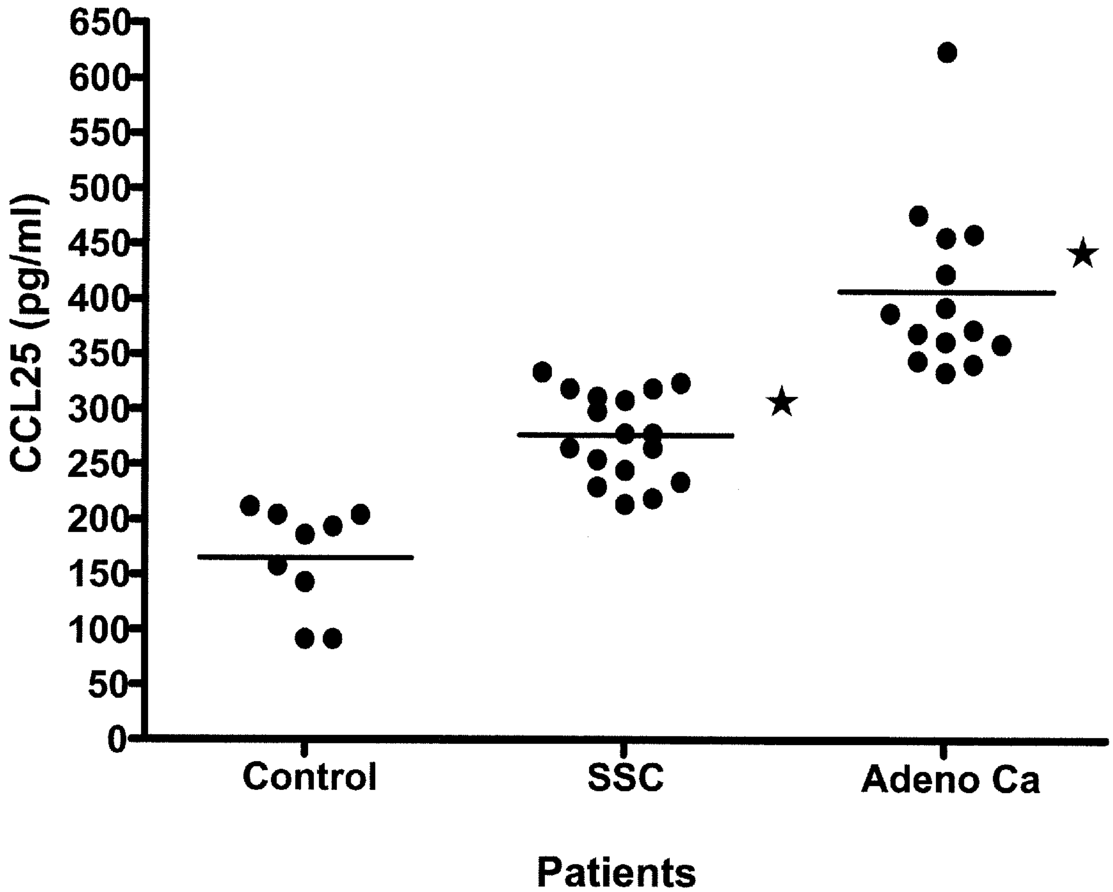


FIG. 22



650
600
550
500
450
400
350
300
250
200
150
100
50
0
CCL25 (pg/ml)
Control
SSC
Adeno Ca
Patients

FIG. 23

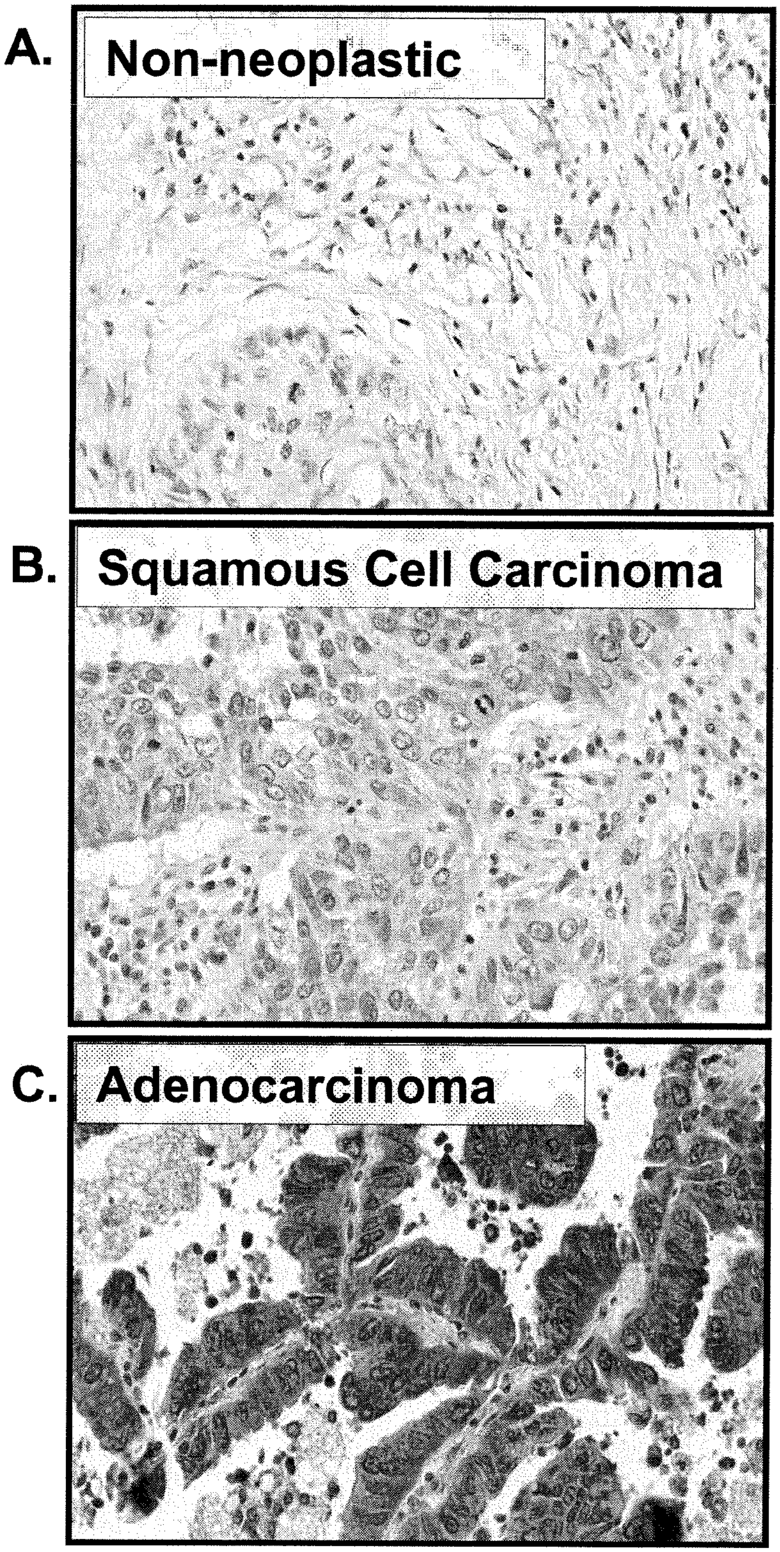

A.
Non-neoplastic
B.
Squamous Cell Carcinoma
C.
Adenocarcinoma

FIG. 24

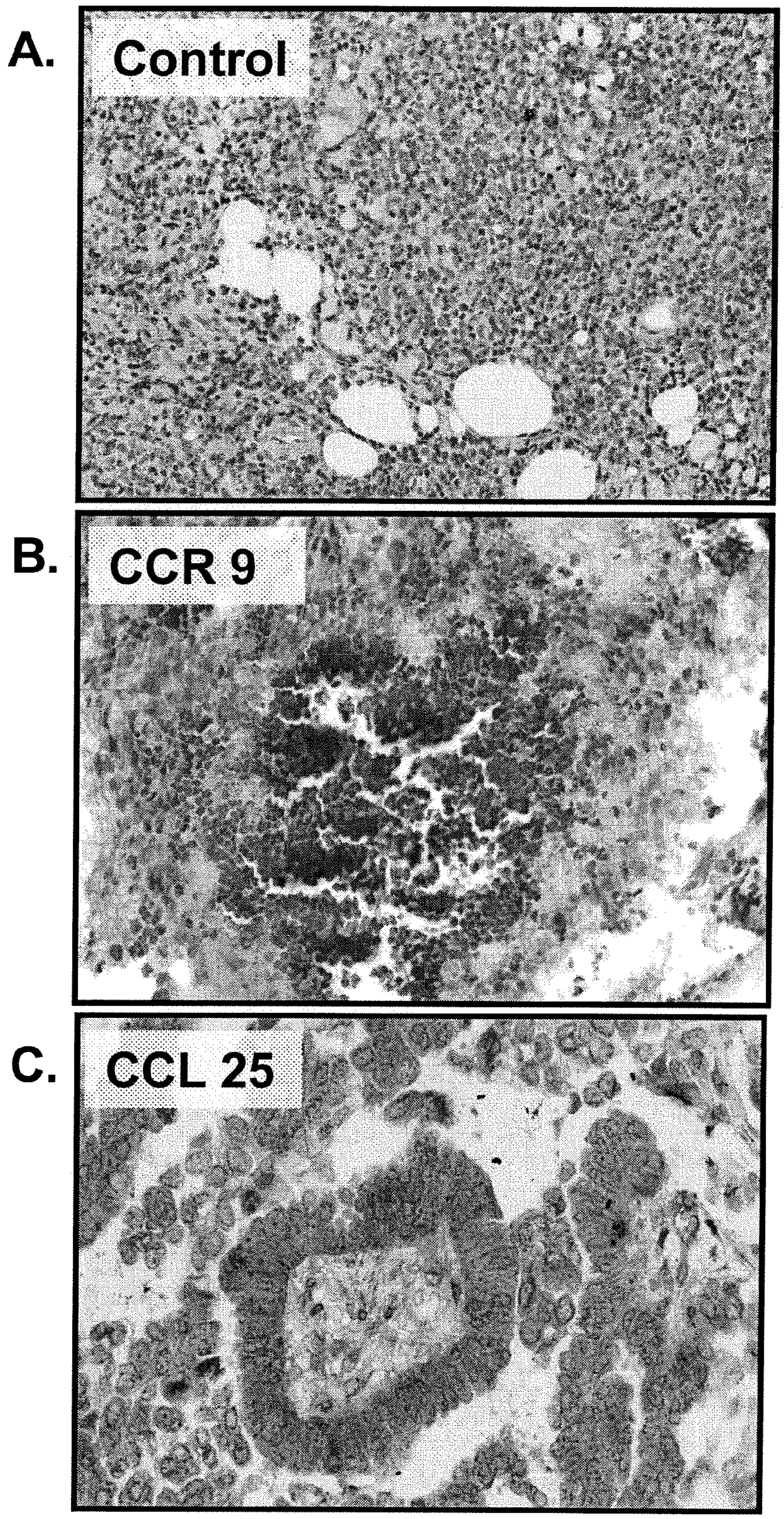


FIG. 25

ANTI-CCL25 AND ANTI-CCR9 ANTIBODIES FOR THE PREVENTION AND TREATMENT OF CANCER AND CANCER CELL MIGRATION

This application is a Continuation-In-Part of U.S. patent application Ser. No. 13/248,904, filed on Sep. 29, 2011, which is a Continuation-In-Part of U.S. patent application Ser. No. 13/233,769, filed on Sep. 15, 2011, which is a Continuation-In-Part of U.S. patent application Ser. No. 12/967, 273, filed Dec. 14, 2010, which is a continuation of U.S. patent application Ser. No. 10/712,398, filed on Nov. 14, 2003, now U.S. Pat. No. 7,919,083, which claims priority of U.S. Provisional Patent Application No. 60/426,347, filed Nov. 15, 2002. The entirety of all of the aforementioned applications is incorporated herein by reference.

FIELD

This application generally relates to the fields of antibodies. In particular, the application relates to the use of anti-chemokine and/or anti-chemokine receptor antibodies for the inhibition or prevention of the growth and/or migration of cancer cells.

BACKGROUND

Despite recent advances in cancer research, the development of cell-specific therapies for the treatment of malignancies remain elusive. The many and complex factors that enable malignant cells to undergo mutations, evade immune protection and promote angiogenesis to deliver nutrients to the rapidly growing cells complicate the development of targeted treatment modalities. Current therapies have multiple untoward side effects. For example, chemotherapy results in multiple painful and sometimes lethal side effects. Advances in biotechnology have promoted the development of targeted biologicals with fewer side effects.

Host cells have surface receptors that associate with ligands to signal and cause host cell activities. The epidermal growth factor receptor helps control cell growth and metastasis. Many tumor cells express higher numbers of epidermal growth factor receptors than normal cells. A new treatment designated IMC-225 was specifically designed to target and block epidermal growth factor receptors, thus preventing cell division and repair. Recently, trastuzumab, which is a HER-2-specific monoclonal antibody, has proven effective at treating metastatic breast cancers. This antibody blocks interactions on cancer cells that inhibit cell growth. HER-2, however, is only found on about 25 to 30 percent of breast cancer cells.

Chemokines are a superfamily of small, cytokine-like proteins that are resistant to hydrolysis, promote neovascularization or endothelial cell growth inhibition, induce cytoskeletal rearrangement, activate or inactivate lymphocytes, and mediate chemotaxis through interactions with G-protein coupled receptors. Chemokines can mediate the growth and migration of host cells that express their receptors.

Chemokine (C-C motif) ligand 25 (CCL25), also known as Thymus-Expressed Chemokine (TECK), is a small cytokine belonging to the CC chemokine family. CCL25 is chemotactic for thymocytes, macrophages, and dendritic cells. CCL25 elicits its effects by binding the chemokine receptors CCR9 and is believed to play a role in the development of T-cells. Human CCL25 is produced as a protein precursor containing 151 amino acids. The gene for CCL25 (scya25) is located on human chromosome 19.

Chemokine (C-C motif) receptor 9 (CCR9), also known as GPR 9-6, is very highly expressed in thymus (on both immature and mature T-cells) while low in lymph nodes and spleen. CCR9 is also abundant in the gut, with its expression associated with T cells of the intestine. To note, the chemokine binding protein D6 had previously been referred to as CCR9, but this molecule is a scavenger receptor not a true (signaling) chemokine receptor.

SUMMARY

One aspect of the present application relates to a method for treating blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma or germ cell tumor in a subject. In one embodiment, the method comprises the step of administering to the subject a therapeutically effective amount of an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof, wherein said therapeutically effective amount is between about 0.5 and 50 mg/kg. In another embodiment, the method comprises the step of immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) as protein, peptide or encoded gene to induce antibodies that inhibit the biological activity of CCL25 and/or CCR9.

Another aspect of the present application relates to a method for treating cancer in a subject, comprising: administering to said subject an effective amount of an expression vector that expresses an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof in said subject, wherein the cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma or germ cell tumor.

Another aspect of the present application relates to a method for treating or preventing cancer in a subject, comprising: administering to the subject an effective amount of an expression vector that expresses an agent that (1) inhibits the expression of CCL25 and/or CCR9, or (2) inhibits the interaction between CCL25 and CCR9, or (3) inhibits a biological activity of CCL25 and/or CCR9, wherein the cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, or sarcoma, or germ cell tumor.

Another aspect of the present application relates to a method for prevention or inhibition of the migration or metastasis of cancer cells with elevated expression of CCL25 and/or CCR9 in a subject. In one embodiment, the method comprises the step of administering to the subject a therapeutically effective amount of an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof, wherein the therapeutically effective amount is between about 0.5 and 50 mg/kg. In another embodiment, the method comprises the step of immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) as protein, peptide or encoded gene to induce antibodies that inhibit the biological activity of CCL25 and/or CCR9. In another embodiment, the method comprises the step of administering to the subject an expression vector that expresses an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof.

Another aspect of the present application relates to a method for enhancing the effect of chemotherapy. In one embodiment, the method comprises the step of administering to a subject who is under chemotherapy for a cancer, an effective amount of an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof, wherein said effective amount is between about 0.5 and 50 mg/kg, wherein said cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, or germ cell tumor. In another embodiment, the method comprises the step of immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) as protein, peptide or encoded gene to induce antibodies that inhibit the biological activity of CCL25 and/or CCR9. In another embodiment, the method comprises the step of administering to the subject an expression vector that expresses an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof in said subject.

Another aspect of the present application relates to a method for enhancing the effect of chemotherapy. The method comprises administering to a subject who is under chemotherapy for a cancer an effective amount of an expression vector that expresses an agent capable of (1) inhibiting the expression of CCL25 and/or CCR9, or (2) inhibiting the interaction between CCL25 and CCR9, or (3) inhibiting a biological activity of CCL25 and/or CCR9, wherein the cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma or germ cell tumor.

Another aspect of the present application relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an expression vector capable of expressing an agent that (1) inhibits the expression of CCL25 and/or CCR9, or (2) inhibits the interaction between CCL25 and CCR9, or (3) inhibits a biological activity of CCL25 and/or CCR9.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows CCL25 expression by breast cancer tissue.

FIG. **2** shows that CCL25 inhibits cisplatin-induced reductions in breast cancer cell line growth.

FIG. **3**A-B shows that CCL25 protects breast cancer cells from cisplatin-induced apoptosis.

FIGS. **4**A-B show PI3K and Akt activation by CCL25-CCR9 interactions in a breast cancer cell line.

FIGS. **5**A-B show GSK-3β and FKHR phosphorylation following CCL25 treatment of a breast cancer cell line.

FIG. **6** shows CCR9 and CCL25 expression by ovarian cancer tissues.

FIGS. **7**A-B show an analysis of CCL25 expression by ovarian cancer tissues.

FIGS. **8**A-B show an analysis of CCR9 expression by ovarian cancer tissues.

FIGS. **9**A-B show CCR9 and CCL25 expression by ovarian cancer cell lines.

FIGS. **10**A-B show hypoxia-regulated CCR9 mRNA and surface protein expression by ovarian cancer cells.

FIGS. **11**A-B show hypoxia-mediated and CCL25-mediated migration and invasion of SKOV-3 cells.

FIGS. **12**A-B show CCL25-induced collagenase expression by SKOV-3 cells.

FIGS. **13**A-B show CCL25-induced gelatinase expression by SKOV-3 cells.

FIGS. **14**A-B show CCL25-induced stromelysin expression by SKOV-3 cells.

FIG. **15** shows CCR9 expression by prostate cancer cells.

FIGS. **16**A-D show CCR9 expression by prostate tissue.

FIGS. **17**A-D show CCL25 expression by prostate cancer tissue.

FIG. **18** shows serum CCL25 levels in normal healthy donors or patients with prostatic disease.

FIGS. **19**A-C show CCL25 expression by mouse bone marrow cells.

FIGS. **20**A-B show CCR9-mediated prostate cancer cell migration and invasion.

FIG. **21** shows CCL25-induced active MMP expression by prostate cancer cell lines.

FIGS. **22**A-F show inhibition of bone metastasis of PC3 prostate cancer cell line by CCR9 knockdown.

FIG. **23** shows serum CCL25 levels in lung cancer patients.

FIGS. **24**A-C show CCR9 expression by non-neoplastic lung and lung cancer tissues.

FIGS. **25**A-C show CCR9-CCL25 expression by colon cancer tissues.

DETAILED DESCRIPTION

The following detailed description is presented to enable any person skilled in the art to make and use the invention. For purposes of explanation, specific nomenclature is set forth to provide a thorough understanding of the present application. However, it will be apparent to one skilled in the art that these specific details are not required to practice the invention. Descriptions of specific applications are provided only as representative examples. The present application is not intended to be limited to the embodiments shown, but is to be accorded the widest possible.

Unless otherwise defined, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

DEFINITIONS

As used herein, the following terms shall have the following meanings:

The terms "treat," "treating" or "treatment" as used herein, refers to a method of alleviating or abrogating a disorder and/or its attendant symptoms. The terms "prevent", "preventing" or "prevention," as used herein, refer to a method of barring a subject from acquiring a disorder and/or its attendant symptoms. In certain embodiments, the terms "prevent," "preventing" or "prevention" refer to a method of reducing the risk of acquiring a disorder and/or its attendant symptoms.

As used herein, the term "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. The term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired biological activity. By "specifically bind" or "immunoreacts with" is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react (i.e., bind) with other polypeptides or binds at much lower affinity with other polypeptides. The term "antibody" also includes antibody fragments that comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody (scFv) molecules; and multispecific antibodies formed from antibody fragments. In certain embodiments of the invention, it may be desirable to use an antibody fragment, rather than an intact antibody, to increase tumor penetration, for example. In this case, it may be desirable to use an antibody fragment that has been modified by any means known in the art in order to increase its serum half life.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

"Humanized" forms of non-human antibodies are chimeric antibodies which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and/or capacity. Methods for making humanized and other chimeric antibodies are known in the art.

"Bispecific antibodies" are antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for CXCL16 or CXCR6. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit. Methods for making bispecific antibodies are known in the art.

The use of "heteroconjugate antibodies" is also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents.

The present invention also contemplates the use of "immunoconjugates" comprising an antibody conjugated to a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate). Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *momordica charantia* inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include 212Bi, 131I, 131In, 90Y, and 186Re.

In a pharmacological sense, in the context of the present invention, a "therapeutically effective amount" of an antibody refers to an amount effective in the prevention or treatment of a disorder for the treatment of which the antibody is effective. A "disorder" is any condition that would benefit from treatment with the antibody, including carcinoma and chemoresistance. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question.

The term "tumor" as used herein refers to a neoplasm or a solid lesion formed by an abnormal growth of cells. A tumor can be benign, pre-malignant or malignant.

The term "cancer" is defined as a malignant neoplasm or malignant tumor and is a class of diseases in which a group of cells display uncontrolled growth, invasion that intrudes upon and destroys adjacent tissues, and sometimes metastasis, or spreading to other locations in the body via lymph or blood. These three malignant properties of cancers differentiate them from benign tumors, which do not invade or metastasize. Exemplary cancers include: carcinoma, melanoma, sarcoma, lymphoma, leukemia, germ cell tumor, and blastoma.

The term "carcinoma" as used herein refers to an invasive malignant tumor consisting of transformed epithelial cells or transformed cells of unknown histogenesis, but which possess specific molecular or histological characteristics that are associated with epithelial cells, such as the production of cytokeratins or intercellular bridges. Exemplary carcinomas of the present invention include ovarian cancer, vaginal cancer, cervical cancer, uterine cancer, prostate cancer, anal cancer, rectal cancer, colon cancer, stomach cancer, pancreatic cancer, insulinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine tumor, breast cancer, lung cancer, esophageal cancer, oral cancer, brain cancer, medulloblastoma, neuroectodermal tumor, glioma, pituitary cancer, and bone cancer.

The term "lymphoma" as used herein is a cancer of lymphatic cells of the immune system. Lymphomas typically present as a solid tumor. Exemplary lymphomas include: small lymphocytic lymphoma, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, MALT lymphoma, nodal marginal zone B cell lymphoma (NMZL), follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma, B cell chronic lymphocytic lymphoma, classical Hodgkin lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, adult T cell lymphoma, nasal type extranodal NK/T cell lymphoma, enteropathy-type T cell lymphoma, hepatosplenic T cell lymphoma, blastic NK cell lymphoma, mycosis fungoide, Sezary syndrome, primary cutaneous CD30-positive T cell lympho-proliferative disorders, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, angioimmunoblastic T cell lymphoma, unspecified peripheral T cell lymphoma, and anaplastic large cell lymphoma. Exemplary forms of classical Hodgkin lymphoma including: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted or not depleted

The term "sarcoma" as used herein is a cancer that arises from transformed cells in one of a number of tissues that develop from embryonic mesoderm. Thus, sarcomas include tumors of bone, cartilage, fat, muscle, vascular, and hematopoietic tissues. For example, osteosarcoma arises from bone, chondrosarcoma arises from cartilage, liposarcoma arises from fat, and leiomyosarcoma arises from smooth muscle. Exemplary sarcomas include: Askin's tumor, botryodies, chondrosarcoma, Ewing's-PNET, malignant Hemangioendothelioma, malignant Schwannoma, osteosarcoma, soft tissue sarcomas. Subclases of soft tissue sarcomas include: alveolar soft part sarcoma, angiosarcoma, cystosarcoma phyllodes, dermatofibrosarcomadesmoid tumor, desmoplastic small round cell tumor, epithelioid sarcomaextraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcomal, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, and synovial sarcoma.

The term "leukemia" as used herein is a cancer of the blood or bone marrow characterized by an abnormal increase of white blood cells. Leukemia is a broad term covering a spectrum of diseases. In turn, it is part of the even broader group of diseases called hematological neoplasms. Leukemia is subdivided into a variety of large groups; the first division is between acute and chronic forms of leukemia. Acute leukemia is characterized by a rapid increase in the numbers of immature blood cells. Crowding due to such cells makes the bone marrow unable to produce healthy blood cells. Chronic leukemia is characterized by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Leukemia is also subdivided by the blood cells affected. This split divides leukemias into lymphoblastic or lymphocytic leukemias and myeloid or myelogenous leukemias. In lymphoblastic or lymphocytic leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes. In myeloid or myelogenous leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets. Combining these two classifications provides a total of four main categories. Within each of these four main categories, there are typically several subcategories. There are also rare types outside of this classification scheme. Exemplary leukemias include: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), hairy cell leukemia (HCL), T-cell prolymphocytic leukemia, large granular lymphocytic leukemia, juvenile myelomonocytic leukemia, B-cell prolymphocytic leukemia, Burkitt leukemia, and adult T-cell leukemia.

The term "melanoma" as used herein is a cancer or malignant tumor of melanocytes. Melanocytes are cells that produce the dark pigment, melanin, which is responsible for the color of skin. They predominantly occur in skin, but are also found in other parts of the body, including the bowel and the eye. Melanoma is divided into the following stereotypes and subtypes: lentigo maligna, lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, mucosal melanoma, nodular melanoma, polypoid melanoma, desmoplastic melanoma, amelanotic melanoma, soft-tissue melanoma, melanoma with small nevus-like cells, melanoma with features of a Spitz nevus, and uveal melanoma.

The term "germ cell tumor (GCT)" as used herein is a neoplasm derived from germ cells. Germ cell tumors can be cancerous or non-cancerous tumors. Germ cells normally occur inside the gonads (ovary and testis). Germ cell tumors that originate outside the gonads may be birth defects resulting from errors during development of the embryo. Germ cell tumors are broadly divided in two classes: germinomatous or seminomatous and nongerminomatous or nonseminomatous germ cell tumors. Exemplary germinomatous or seminomatous germ cell tumors include: germinoma, dysgerminoma, and seminoma. Exemplary nongerminomatous or nonseminomatous germ cell tumors include: Embryonal carcinoma, endodermal sinus tumor or yolk sac tumor (EST, YST), choriocarcinoma, mature teratoma, dermoid cyst, immature teratoma, teratoma with malignant transformation, polyembryoma, gonadoblastoma, and mixed GCT.

The term "metastasis" as used herein refers to the spread of a cancer or carcinoma from one organ or part to another non-adjacent organ or part.

The term "mammal" refers to any animal classified as a mammal, including humans, non-human primates, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

The term "inhibits" is a relative term, an agent inhibits a response or condition if the response or condition is quantitatively diminished following administration of the agent, or if it is diminished following administration of the agent, as compared to a reference agent. Similarly, the term "prevents" does not necessarily mean that an agent completely eliminates the response or condition, so long as at least one characteristic of the response or condition is eliminated. Thus, a composition that reduces or prevents an infection or a response, such as a pathological response, can, but does not necessarily completely eliminate such an infection or response, so long as the infection or response is measurably diminished, for example, by at least about 50%, such as by at least about 70%, or about 80%, or even by about 90% of (that is to 10% or less than) the infection or response in the absence of the agent, or in comparison to a reference agent.

The term "increased level" refers to a level that is higher than a normal or control level customarily defined or used in the relevant art. For example, an increased level of immunostaining in a tissue is a level of immunostaining that would be considered higher than the level of immunostaining in a control tissue by a person of ordinary skill in the art.

The term "CXCL13 immunogen" and "CXCR5 immunogen" refers to an immunogenic composition comprising (1) an immunogenic peptide derived from CXCL13 or CXCR5 and/or (2) an expression vector that encodes, and is capable of expressing, an immunogenic peptide derived from CXCL13 or CXCR5. The immunogenic peptide derived from CXCL13 or CXCR5 may be fused to another moiety to enhance its immunogenicity. Examples of the CXCL13 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of RSSSTLPVPVFKRKIP (SEQ ID NO:45), PRGNGCPRKEIIVWKK (SEQ ID NO:46), LPRGNGCPRKEIIVWK (SEQ ID NO:47), QILPRGNGCPRKEIIV (SEQ ID NO:48), ILPRGNGCPRKEIIVW (SEQ ID NO:49), RIQILPRGNGCPRKEI (SEQ ID NO:50), RGNGCPRKEIIVWKKN (SEQ ID NO:51), KRSSSTLPVPVFKRKI (SEQ ID NO:52), IQILPRGNGCPRKEII (SEQ ID NO:53), DRIQILPRGNGCPRKE (SEQ ID NO:54), RKRSSSTLPVPVFKRK (SEQ ID NO:55), RCRCVQESSVFIPRRF (SEQ ID NO:56), GNGCPRKEIIVWKKNK (SEQ ID NO:57), CVQESSVFIPRRFIDR (SEQ ID NO:58), IDRIQILPRGNGCPRK (SEQ ID NO:59), LRCRCVQESSVFIPRR (SEQ ID NO:60), FIDRIQILPRGNGCPR (SEQ ID NO:61), RCVQESSVFIPRRFID (SEQ ID NO:62), CRCVQESSVFIPRRFI (SEQ ID NO:63), QESSVFIPRRFIDRIQ (SEQ ID NO:64), RFIDRIQILPRGNGCP (SEQ ID NO:65), VQESSVFIPRRFIDRI (SEQ ID NO:66), ESSVFIPRRFIDRIQI (SEQ ID NO:67), SLRCRCVQESSVFIPR (SEQ ID NO:68), NGCPRKEIIVWKKNKS (SEQ ID NO:69), PQAEWIQRMMEVLRKR (SEQ ID NO:70), RRFIDRIQILPRGNGC (SEQ ID NO:71), LRKRSSSTLPVPVFKR (SEQ ID NO:72), VQESSVFIPRR (SEQ ID NO:73, EWIQRMMEVLRKRSSSTLPVPVFKRK (SEQ ID NO:74), KKNK (SEQ ID NO:75), RKRSSS (SEQ ID NO:76), RGNGCP (SEQ ID NO:77), VYYTSLRCRCVQESSVFIPRR (SEQ ID NO:78), DRIQILP (SEQ ID NO:79), RKEIIVW (SEQ ID NO:80) and KSIVCVDPQ (SEQ ID NO:81). Examples of the CXCR5 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of TSLVENHLCPATE (SEQ ID NO:82), EGSVGWVLGTFLCKT (SEQ ID NO:83), LPRCTFS (SEQ ID NO:84), LARLKAVDNT (SEQ ID NO:85) and MASFKAVFVP (SEQ ID NO:86).

The term "CXCL16 immunogen" and "CXCR6 immunogen" refers to an immunogenic composition comprising (1) an immunogenic peptide derived from CXCL16 or CXCR6 and/or (2) an expression vector that encodes, and is capable of expressing, an immunogenic peptide derived from CXCL16 or CXCR6. The immunogenic peptide derived from CXCL16 or CXCR6 may be in the form of a fusion protein to enhance its immunogenicity. Examples of the CXCL16 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of AAGPEAGENQKQPEKN (SEQ ID NO:87), SQASEGASSDIHTPAQ (SEQ ID NO:88), STLQSTQRPTLPVGSL (SEQ ID NO:89), SWSVCGGNKDPWVQEL (SEQ ID NO:90), GPTARTSATVPVLCLL (SEQ ID NO:91), SGIVAHQKHLLPTSPP (SEQ ID NO:92), RLRKHL (SEQ ID NO:93), LQSTQRP (SEQ ID NO:94), SSDKELTRPNETT (SEQ ID NO:95), AGENQKQPEKNA (SEQ ID NO:96), NEGSVT (SEQ ID NO:97), ISSDSPPSV (SEQ ID NO:98), CGGNKDPW (SEQ ID NO:99), LLPTSPPISQASEGASSDIHT (SEQ ID NO:100), STQRPTLPVGSLSSDKELTRPNETTIHT (SEQ ID NO:101), SLAAGPEAGENQKQPEKNAGPTARTSA (SEQ ID NO:102), TGSCYCGKR (SEQ ID NO:103), DSPPSVQ (SEQ ID NO:104), RKHLRAYHRCLYYTRFQLLSWSVCGG (SEQ ID NO:105), WVQELMSCLDLKECGHAYSGIVAHQKHLLPTSPPISQ (SEQ ID NO:106), SDIHTPAQMLLSTLQ (SEQ ID NO:107), RPTLPVGSL (SEQ ID NO:108), TAGHSLAAG (SEQ ID NO:109), GKRISSDSPPSVQ (SEQ ID NO:110) and KDPWVQELMSCLDLKECGHAYSGIVAHQKH (SEQ ID NO:111). Examples of the CXCR6 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of HQDFLQFSKV (SEQ ID NO:112), AGIHEWVFGQVMCK (SEQ ID NO:113), PQIIYGNVFNLDKLICGYHDEAI (SEQ ID NO:114) and YYAMTSFHYTIMVTEA (SEQ ID NO:115).

The term "CCL25 immunogen" and "CCR9 immunogen" refers to an immunogenic composition comprising (1) an immunogenic peptide derived from CCL25 or CCR9 and/or (2) an expression vector that encodes, and is capable of expressing, an immunogenic peptide derived from CCL25 or CCR9. The immunogenic peptide derived from CCL25 or CCR9 may be in the form of a fusion protein to enhance its immunogenicity. Examples of the CCL25 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of LAYHYPIGWAVL (SEQ ID NO:116), KRHRKVCGNPKSREVQRAMKLLDARNKVFAKLHH (SEQ ID NO:117), FEDCCLAYHYPIGWAVLRRA (SEQ ID NO:118), IQEVSGSCNLPAAIFYLPKRHRKVCGN (SEQ ID NO:119), AMKLLDAR (SEQ ID NO:120), KVFAKLHHN (SEQ ID NO:121), QAGPHAVKKL (SEQ ID NO:122), FYLPKRHRKVCGNP (SEQ ID NO:123) YLPKRHRKVCGNPK (SEQ ID NO:124), LPKRHRKVCGNPKS (SEQ ID NO:125), PKRHRKVCGNPKSR (SEQ ID NO:126), CGNPKSREVQRAMK (SEQ ID NO:127), GNPKSREVQRAMKL (SEQ ID NO:128), KFSNPISSSKRNVS (SEQ ID NO:129), PKSREV (SEQ ID NO:130), LHHNTQT (SEQ ID NO:131) and SSSKRN (SEQ ID NO:132). Examples of the CCR9 immunogenic peptides include, but are not limited to, peptides consisting of, or comprising, one or more sequences selected from the group consisting of QFASHFLPP (SEQ ID NO:133), AAADQWKFQ (SEQ ID NO:134), TFMCKVVNSM (SEQ ID NO:135), IAICTMVYPS (SEQ ID NO:136) and VQTIDAYAMFISNCAVSTNIDICFQ (SEQ ID NO:137).

The term "biological sample," as used herein, refers to material of a biological origin, which may be a body fluid or body product such as blood, plasma, urine, saliva, spinal fluid, stool, sweat or breath. Biological sample also includes tissue samples and cell samples.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed that "less than or equal to" the value, "greater than or equal to the value" and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed the "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed.

Treating or Preventing Cancer by Immunizing Against CCL25 and/or CCR9

CCL25 is a ligand for the CCR9 chemokine receptor. Both the chemokine and the receptor appear to play a role in the regulation of metastasis and invasion of cancer. Both CCL25 and CCR9 are locally up-regulated in multiple carcinoma tissue types compared to normal tissues, including ovarian, lung, breast, prostate, colon, bone and pancreatic cancers. CCL25 levels are also increased in the serum of patients with those cancers. Additionally, soluble CCL25 chemokine enhances both in vivo and in vitro proliferation and migration of cancer cells.

CCR9 is a member of the chemokine receptor family of G protein coupled receptors (GPCRs) that may have a diverse role in cancer cell survival that presumably supports protection against chemotherapeutic drugs. Interaction of CCR9 with CCL25 modulates matrix metalloproteinase (MMP) expression and enhances the migration and invasive potential of carcinoma cells. This suggests that CCR9-CCL25 interaction contributes to carcinoma cell migration and invasion. Accordingly, blocking this axis has the potential to inhibit carcinoma cell metastasis.

One aspect of the present application relates to a method for treating or preventing cancer by immunizing against CCL25 and/or CCR9. The method comprises the step of immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) as protein, peptide or polynucleotide encoding the same, to induce antibodies that inhibit the biological activity of CCL25 and/or CCR9, wherein the cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, or sarcoma.

In another embodiment, the method comprises the step of immunizing the subject with an effective amount of (1) one or more CCL25 and CCR9 immunogen(s) as protein, peptide or polynucleotide encoding the same, and (2) one or more CXCL13 and CXCR5 immunogen(s) as protein, peptide or polynucleotide encoding the same, and/or one or more CXCL16 and CXCR6 immunogen(s) as protein, peptide or polynucleotide encoding the same.

Methods for Treating or Preventing Cancer Using Anti-CCL25 and Anti-CCR9 Antibodies.

Another aspect of the present application relates to methods for treating or preventing cancer using an anti-CCL25 antibody and/or an anti-CCR9 antibody. The method comprises administering to an subject in need of such treatment, a therapeutically effective amount of an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof, wherein the cancer is blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, or sarcoma.

In another embodiment, the subject is diagnosed with a cancer that results in elevated CCL25 and/or CCR9 expression in the cancer cells. Examples of such cancer include, but are not limited to, blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma and germ cell tumor. In one embodiment, the subject is diagnosed with brain cancer. In another embodiment, the subject is diagnosed with bone cancer. In another embodiment, the subject is diagnosed with pituitary cancer. In yet another embodiment, the subject is diagnosed with ovarian cancer.

In another embodiment, the method further comprises determining the level of CCL25 and/or CCR9 expression in a tissue from the subject and, if an increased level of CCL25 and/or CCR9 is detected, administering to the subject a therapeutically effective amount of an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof.

In another embodiment, the method further comprises determining the level of CCL25 and/or CCR9 expression in a tissue from the subject and, if an increased level of CCL25 and/or CCR9 is detected, immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) as protein, peptide or encoded gene to induce antibodies that inhibit the biological activity of CCL25 and/or CCR9.

In another embodiment, the method further comprises determining the level of CCL25 and/or CCR9 expression in a tissue from the subject and, if an increased level of CCL25 and/or CCR9 is detected, immunizing the subject with an effective amount of (1) one or more CCL25 and CCR9 immunogen(s) as protein, peptide or encoded gene, and (2) one or more CXCL13 and CXCR5 immunogen(s) as protein, peptide or encoded gene, and/or one or more CXCL16 and CXCR6 immunogen(s) as protein, peptide or encoded gene.

A preferred antibody of the present application is one which binds to human CCL25 and preferably blocks (partially or completely) the ability of CCL25 to bind to a receptor, including, but not limited to, CCR9. Another preferred antibody of the present application is one which binds to human CCR9 and preferably blocks (partially or completely) the ability of a cell, such as a tumor or carcinoma cell, expressing the CCR9 chemokine receptor at its cell surface to bind to a ligand, including, but not limited to, CCL25. Yet another preferred antibody of the present application is one which binds to human CCR9 and preferably blocks (partially or completely) the ability of soluble CCR9 chemokine receptor to bind to a ligand, including, but not limited to, CCL25.

In one embodiment, the anti-CCL25 antibody and/or anti-CCR9 antibody is a monoclonal antibody. In another embodiment, the anti-CCL25 antibody and/or anti-CCR9 antibody is a humanized antibody. In another embodiment, the anti-CCL25 antibody and/or anti-CCR9 antibody is a humanized antibody fragment.

In particular embodiments of the present application, treatment of a subject with an anti-CCL25 and/or anti-CCR9 antibody is in conjunction with the treatment of the subject beforehand, at the same time, or afterward with a therapeutically effective amount of at least one other antibody that is specific for another antigen. In one embodiment, the another antigen is another chemokine or chemokine receptor, such as CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5a, CXCR5b, CXCR6, CXCR7, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL24, CCL27, CCL28, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR10, CCR11, XCL1, XCL2, XCR1, CX3CR1, or CX3CL1.

In another embodiment, the another antigen is a chemokine or chemokine receptor associated with a carcinoma and selected from the group consisting of CCL1, CCL2, CCL4, CCL17, CCL19, CCL21, CCL22, CXCL12, CXCL13, CXCL16, CCR2, CCR7, CCR8, CXCR4, CXCR5, CXCR6, CXCR7, and CX3CR1.

In another embodiment, the another antigen is a chemokine or chemokine receptor associated with a melanoma and selected from the group consisting of CCL27, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCL12, CXCL13, CXCL16, CX3CL1, CCR10, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7, CX3CL1 and CX3CR1.

In another embodiment, the another antigen is a chemokine or chemokine receptor associated with a leukemia and selected from the group consisting of CCL1, CCL4, CCL17, CCL19, CCL21, CCL22, CXCL12, CCR7, CCR8, CXCR4, CXCR7 and CX3CR1.

Other exemplary antigens include molecules such as renin; a growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; a-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIII, factor IX, tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or human urine or tissue-type plasminogen activator (t-PA); bombesin; thrombin; hemopoietic growth factor; tumor necrosis factor-α and -β; enkephalinase; a serum albumin such as human serum albumin; Muellerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a microbial protein, such as beta-lactamase; DNase; IgE; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); members of the ErbB receptor family such as the EGF receptor; transforming growth factor (TGF) such as TGF-α and TGF-β, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-α, -β, and -γ; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9 and/or IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; αv/β integrin including either a or b subunits thereof, such as CD11a, CD11b, CD11c, CD18, an ICAM, VLA-4 and VCAM; prostate specific antigen (PSA); a tumor associated antigen such as carcinoembryonic antigen (CEA), CK2, CAl25, TA90, HER2, HER3 or HER4 receptor; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; mpl receptor; CTLA-4; protein C; any one of the proteins from the classical, lectin or alternative complement pathways; and fragments of any of the above-listed polypeptides.

The antibody may be administered to the subject with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. In certain embodiments, the antibody is administered directly to a tumor or cancer tissue, including administration directly to the tumor bed during invasive procedures. The antibody may also be placed on a solid support such as a sponge or gauze for administration against the target chemokine to the affected tissues.

Antibodies of the invention can be administered in the usually accepted pharmaceutically acceptable carriers. Acceptable carriers include, but are not limited to, saline, buffered saline, glucose in saline. Solid supports, liposomes, nanoparticles, microparticles, nanospheres or microspheres may also be used as carriers for administration of the antibodies.

The appropriate dosage ("therapeutically effective amount") of the antibody will depend, for example, on the condition to be treated, the severity and course of the condition, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, the type of antibody used, and the discretion of the attending physician. The antibody is suitably administered to the patent at one time or over a series of treatments and may be administered to the patent at any time from diagnosis onwards. The antibody may be administered as the sole treatment or in conjunction with other drugs or therapies useful in treating the condition in question.

As a general proposition, the therapeutically effective amount of the antibody administered will be in the range of about 1 ng/kg body weight/day to about 100 mg/kg body weight/day whether by one or more administrations. In a particular embodiments, the range of antibody administered is from about 1 ng/kg body weight/day to about 1 μg/kg body weight/day, 1 ng/kg body weight/day to about 100 ng/kg body weight/day, 1 ng/kg body weight/day to about 10 ng/kg body weight/day, 10 ng/kg body weight/day to about 1 μg/kg body weight/day, 10 ng/kg body weight/day to about 100 ng/kg body weight/day, 100 ng/kg body weight/day to about 1 μg/kg body weight/day, 100 ng/kg body weight/day to about 10 μg/kg body weight/day, 1 μg/kg body weight/day to about 10 μg/kg body weight/day, 1 μg/kg body weight/day to about 100 μg/kg body weight/day, 10 μg/kg body weight/day to about 100 μg/kg body weight/day, 10 μg/kg body weight/day to about 1 mg/kg body weight/day, 100 μg/kg body weight/day to about 10 mg/kg body weight/day, 1 mg/kg body weight/day to about 100 mg/kg body weight/day and 10 mg/kg body weight/day to about 100 mg/kg body weight/day.

In another embodiment, the antibody is administered at a dosage range of 1 ng-10 ng per injection, 10 ng to 100 ng per injection, 100 ng to 1 μg per injection, 1 μg to 10 μg per injection, 10 μg to 100 μg per injection, 100 μg to 1 mg per injection, 1 mg to 10 mg per injection, 10 mg to 100 mg per injection, and 100 mg to 1000 mg per injection. The antibody may be injected daily, or every 2, 3, 4, 5, 6 and 7 days, or every 1, 2, 3 or 4 weeks.

In another particular embodiment, the dose range of antibody administered is from about 1 ng/kg to about 100 mg/kg In still another particular embodiment, the range of antibody administered is from about 1 ng/kg to about 10 ng/kg, about 10 ng/kg to about 100 ng/kg, about 100 ng/kg to about 1 μg/kg, about 1 μg/kg to about 10 μg/kg, about 10 μg/kg to about 100 μg/kg, about 100 μg/kg to about 1 mg/kg, about 1 mg/kg to about 10 mg/kg, about 10 mg/kg to about 100 mg/kg, about 0.5 mg/kg to about 30 mg/kg, and about 1 mg/kg to about 15 mg/kg.

In other particular embodiments, the amount of antibody administered is, or is about, 0.0006, 0.001, 0.003, 0.006, 0.01, 0.03, 0.06, 0.1, 0.3, 0.6, 1, 3, 6, 10, 30, 60, 100, 300, 600 and 1000 mg/day. As expected, the dosage will be dependant on the condition, size, age and condition of the patient.

The antibody may be administered, as appropriate or indicated, a single dose as a bolus or by continuous infusion, or as multiple doses by bolus or by continuous infusion. Multiple doses may be administered, for example, multiple times per day, once daily, every 2, 3, 4, 5, 6 or 7 days, weekly, every 2, 3, 4, 5 or 6 weeks or monthly. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques.

In particular embodiments of the present application, therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody may be administered to a subject in need thereof as a sole therapeutic agent. In a particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody to kill or promote apoptosis of the tumor or carcinoma cells. In another particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody inhibits or prevents the establishment of a tumor or carcinoma. In a further particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody inhibits or prevents the migration or metastasis of tumor or carcinoma cells from an existing tumor or carcinoma. In yet another particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody inhibits or prevents the invasion of tumor or carcinoma cells into non-cancerous tissues.

In particular embodiments of the present application, therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody may be administered to a subject in need thereof in conjunction with one or more additional therapeutically effective antibodies. Said one or more additional therapeutically effective antibodies may be directed to additional determinants on CCL25 and/or CCR9, other chemokines, other chemokine receptors, other soluble or cell surface ligands or receptors including, but not limited to, tumor or carcinoma specific antigens, viral, bacterial or parasite antigens, products of cancer cells or remnants of apoptosis. The anti-CCL25 and/or anti-CCR9 antibody may be administered before, concurrently with, and/or after the one or more additional therapeutically effective antibodies.

In a particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody augments the effectiveness of the one or more additional therapeutically effective antibodies in killing tumor or carcinoma cells. In a more particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody reduces the amount of the one or more additional therapeutically effective antibodies required for killing tumor or carcinoma cells.

In a further particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody inhibits or prevents the migration or metastasis of tumor or carcinoma cells from an established tumor or carcinoma, enhancing the local effectiveness of the one or more additional therapeutically effective antibodies in killing tumor or carcinoma cells. In yet another particular embodiment, the therapeutically effective amount of anti-CCL25 and/or anti-CCR9 antibody inhibits or prevents the invasion of tumor or carcinoma cells into non-cancerous tissues, enhancing the local effectiveness of the one or more additional therapeutically effective antibodies in killing tumor or carcinoma cells.

In another embodiment, the anti-CCL25 antibody and/or anti-CCR9 antibody is an antibody conjugated to a cytotoxic agent. In another embodiment, the anti-CCL25 antibody and/or anti-CCR9 antibody is administered with another anti-cancer agent, such as chemotherapy agent.

Another aspect of the present application relates to a method of inhibiting the interaction of the chemokine CCL25 with a cell bearing a receptor thereof. In one embodiment, the method comprises contacting the cell with an effective amount of an antibody or functional fragment thereof which binds to a mammalian CCL25 or a portion of CCL25. In another embodiment, the method comprises the step of immunizing the subject with an effective amount of CCL25 immunogen(s) as protein, peptide or encoded gene to induce antibodies that inhibit the biological activity of CCL25.

Another aspect of the present application relates to a method of inhibiting the interaction of a cell bearing CCR9 with a ligand thereof, comprising contacting the cell with an effective amount of an antibody or functional fragment thereof which binds to a mammalian CCR9 or a portion of CCR9.

In another embodiment, the method of treating cancer comprises administering to an subject in need of such treatment, an effective amount of an expression vector that expresses an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof in a cancer or malignant cell. In another embodiment, the method of treating cancer comprises the step of immunizing the subject with an effective amount of CCL25 and/or CCR9 immunogen(s) to induce the host to produce antibodies that inhibit the biological activity of CCL25 and/or CCR9.

The expression vectors can be any vector that is capable of nucleotide deliver nucleotides encoding an anti-CCL25 antibody and/or an anti-CCR9 antibody into a target cell and express the anti-CCL25 antibody and/or anti-CCR9 antibody in the target cell. In another embodiment, the expression vector is capable of delivering nucleotides encoding CCL25 and/or CCR9 into a target cell to induce the host to produce anti-CXCL13 and/or CXCR5 antibodies. Examples of expression vectors include viral vectors and non-viral vectors. Examples of expression vectors include viral vectors and non-viral vectors.

Viral vectors include, but are not limited to, retrovirus vectors, adenovirus vectors, adeno-associated virus vectors, and other large capacity viral vectors, such as herpes virus and vaccinia virus. Also included are any viral families which share the properties of these viruses which make them suitable for use as expression vectors.

Retroviral Vectors

A retrovirus is an animal virus belonging to the virus family of Retroviridae, including any types, subfamilies, genus, or tropisms. Examples of methods for using retroviral vectors for gene therapy are described in U.S. Pat. Nos. 4,868,116 and 4,980,286; PCT applications WO 90/02806 and WO 89/07136; and Mulligan, (Science 260:926-932 (1993)); the teachings of which are incorporated herein by reference.

Adenoviral Vectors

Recombinant adenoviruses have been shown to achieve high efficiency gene transfer after direct, in vivo delivery to airway epithelium, hepatocytes, vascular endothelium, CNS parenchyma and a number of other tissue sites. Recombinant adenoviruses achieve gene transduction by binding to specific cell surface receptors, after which the virus is internalized by receptor-mediated endocytosis, in the same manner as wild type or replication-defective adenovirus.

A viral vector can be one based on an adenovirus which has had one or more viral genes removed and these virions are generated in a complement cell line, such as the human 293 cell line. In one embodiment, the E1 gene is removed from the adenoviral vector. In another embodiment, both the E1 and E3 genes are removed from the adneoviral vector. In another embodiment, both the E1 and E4 genes are removed from the adneoviral vector. In another embodiment, the adenovirus vector is a gutless adenovirus vector.

Adeno-Associated Viral Vectors

Another type of viral vector is based on an adeno-associated virus (AAV). This defective parvovirus is a preferred vector because it can infect many cell types and is nonpathogenic to humans. AAV type vectors can transport about 4 to 5 kb and wild type AAV is known to stably insert into chromosome 19. Vectors which contain this site specific integration property are preferred. An especially preferred embodiment of this type of vector is the P4.1 C vector produced by Avigen, San Francisco, Calif., which can contain the herpes simplex virus thymidine kinase gene, HSV-tk, and/or a marker gene, such as the gene encoding the green fluorescent protein, GFP.

In another type of AAV virus, the AAV contains a pair of inverted terminal repeats (ITRs) which flank at least one cassette containing a promoter which directs cell-specific expression operably linked to a heterologous gene. Heterologous in this context refers to any nucleotide sequence or gene which is not native to the AAV or B19 parvovirus.

Typically the AAV and B19 coding regions have been deleted, resulting in a safe, noncytotoxic vector. The AAV ITRs, or modifications thereof, confer infectivity and site-specific integration, but not cytotoxicity, and the promoter directs cell-specific expression.

Large Payload Viral Vectors

Molecular genetic experiments with large human herpes viruses have provided a means whereby large heterologous DNA fragments can be cloned, propagated and established in cells permissive for infection with herpes viruses (Sun et al., Nature genetics 8: 33-41, 1994; Cotter and Robertson, Curr Opin Mol Ther 5: 633-644, 1999). These large DNA viruses (herpes simplex virus (HSV) and Epstein-Barr virus (EBV), have the potential to deliver fragments of human heterologous DNA>150 kb to specific cells. EBV recombinants can maintain large pieces of DNA in the infected B-cells as episomal DNA. Individual clones carried human genomic inserts up to 330 kb appeared genetically stable. The maintenance of these episomes requires a specific EBV nuclear protein, EBNA1, constitutively expressed during infection with EBV. Additionally, these vectors can be used for transfection, where large amounts of protein can be generated transiently in vitro. Herpesvirus amplicon systems are also being used to package pieces of DNA>220 kb and to infect cells that can stably maintain DNA as episomes. Other useful systems include, for example, replicating and host-restricted non-replicating vaccinia virus vectors.

Non-Viral vectors include plasmid expression vectors. Plasmid vectors typically include a circular double-stranded DNA loop into which additional DNA segments can be inserted.

In both viral and non-viral expression vectors, the polynucleotide encoding the antibody or antibodies is typically arranged in proximity and orientation to an appropriate transcription control sequence (promoter, and optionally, one or more enhancers) to direct mRNA synthesis. That is, the polynucleotide sequence of interest is operably linked to an appropriate transcription control sequence. Examples of such promoters include: viral promoters such as the immediate early promoter of CMV, LTR or SV40 promoter, polyhedron promoter of baculovirus, *E. coli* lac or trp promoter, phage T7 and lambda P_L promoter, and other promoters known to control expression of genes in eukaryotic cells or their viruses. The promoters may be a tissue specific promoter.

The expression vector typically also contains a ribosome binding site for translation initiation, and a transcription terminator. The vector optionally includes appropriate sequences for amplifying expression. In addition, the expression vectors optionally comprise one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells, such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli.*

The expression vector can also include additional expression elements, for example, to improve the efficiency of translation. These signals can include, e.g., an ATG initiation codon and adjacent sequences. In some cases, for example, a translation initiation codon and associated sequence elements are inserted into the appropriate expression vector simultaneously with the polynucleotide sequence of interest (e.g., a native start codon). In such cases, additional translational control signals are not required. However, in cases where only a polypeptide coding sequence, or a portion thereof, is inserted, exogenous translational control signals, including an ATG initiation codon is provided. The initiation codon is placed in the correct reading frame to ensure translation of the polynucleotide sequence of interest. Exogenous transcriptional elements and initiation codons can be of various origins, both natural and synthetic. If desired, the efficiency of expression can be further increased by the inclusion of enhancers appropriate to the cell system in use.

In one embodiment, the expression vector contains an inducible or regulatable expression system. Examples of regulatable expression systems are briefly described below:

Ecdysone system. The ecdysone system is based on the molting induction system found in *Drosophila*, but modified for inducible expression in mammalian cells. The system uses an analog of the *drosophila* steroid hormone ecdysone, muristerone A, to activate expression of the gene of interest via a heterodimeric nuclear receptor. Expression levels have been reported to exceed 200-fold over basal levels with no effect on mammalian cell physiology.

Progesterone system. The progesterone receptor is normally stimulated to bind to a specific DNA sequence and to activate transcription through an interaction with its hormone ligand. Conversely, the progesterone antagonist mifepristone (RU486) is able to block hormone-induced nuclear transport and subsequent DNA binding. A mutant form of the progesterone receptor that can be stimulated to bind through an interaction with RU486 has been generated. To generate a specific, regulatable transcription factor, the RU486-binding domain of the progesterone receptor has been fused to the DNA-binding domain of the yeast transcription factor GAL4 and the transactivation domain of the HSV protein VP16. The chimeric factor is inactive in the absence of RU486. The addition of hormone, however, induces a conformational change in the chimeric protein, and this change allows binding to a GAL4-binding site and the activation of transcription from promoters containing the GAL4-binding site.

Rapamycin system. Immunosuppressive agents, such as FK506 and rapamycin, act by binding to specific cellular proteins and facilitating their dimerization. For example, the binding of rapamycin to FK506-binding protein (FKBP) results in its heterodimerization with another rapamycin binding protein FRAP, which can be reversed by removal of the drug. The ability to bring two proteins together by addition of a drug potentiates the regulation of a number of biological processes, including transcription. A chimeric DNA-binding domain has been fused to the FKBP, which enables binding of the fusion protein to a specific DNA-binding sequence. A transcriptional activation domain also has been fused to FRAP. When these two fusion proteins are co-expressed in the same cell, a fully functional transcription factor can be formed by heterodimerization mediated by addition of rapamycin. The dimerized chimeric transcription factor can then bind to a synthetic promoter sequence containing copies of the synthetic DNA-binding sequence. This system has been successfully integrated into adenoviral and AAV vectors.

Methods for Treating or Preventing Cancer Using Agents that Inhibits the Expression or Activity of CCL25 or CCR9

Another aspect of the present application relates to methods for treating or preventing cancer by using agents that inhibits the expression or activity of CCL25 or CCR9. In another embodiment, the method comprises administering to an subject in need of such treatment, an effective amount of an expression vector that expresses an agent that (1) inhibits the expression of CCL25 and/or CCR9, or (2) inhibits the interaction between CCL25 and CCR9, or (3) inhibits a biological activity of CCL25 and/or CCR9. In one embodiment, the biological activity of CCL25 and CCR9 includes the interaction between CCL25 and CCR9.

In another embodiment, the subject is diagnosed with a cancer that results in elevated CCL25 and/or CCR9 expression in the cancer cells. Examples of such cancer include, but are not limited to, blastoma, eukemia, lymphoma, melanoma, myeloma, sarcoma, germ cell tumor, and carcinoma such as ovarian cancer, vaginal cancer, cervical cancer, uterine cancer, prostate cancer, anal cancer, rectal cancer, colon cancer, stomach cancer, pancreatic cancer, insulinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine tumor, breast cancer, lung cancer, esophageal cancer, oral cancer, brain cancer, medulloblastoma, neuroectodermal tumor, glioma, pituitary cancer, and bone cancer.

In another embodiment, the method further comprises determining the level of CCL25 and/or CCR9 expression in a tissue from the subject, and administering the agent to the subject only if an increased level of CCL25 and/or CCR9 is detected in the tissue.

In one embodiment, the expression vector is a viral vector. In another embodiment, the expression vector is a non-vector vector. In another embodiment, the expression vector is capable of delivering nucleotides encoding CCL25 and/or CCR9 into a target cell to induce the host to produce anti-CCL25 and/or CCR9 antibodies.

In another embodiment, the agent is an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof.

In yet another embodiment, the agent is a functional nucleic acid. Functional nucleic acids are nucleic acid molecules that have a specific function, such as binding a target molecule or catalyzing a specific reaction. The functional nucleic acid molecules can act as inhibitors of a specific activity possessed by a target molecule. Functional nucleic acid molecules can interact with any macromolecule, such as DNA, RNA and polypeptides. Thus, functional nucleic acids can interact with mRNA or the genomic DNA of CCL25 or CCR9 to inhibit expression or interact with CCL25 or CCR9 protein to inhibit activity. Often functional nucleic acids are designed to interact with other nucleic acids based on sequence homology between the target molecule and the functional nucleic acid molecule. In other situations, the specific recognition between the functional nucleic acid molecule and the target molecule is not based on sequence homology between the functional nucleic acid molecule and the target molecule, but rather is based on the formation of tertiary structure that allows specific recognition to take place. Examples of functional nucleic acid molecules include siRNA, antisense molecules, aptamers, ribozymes, triplex forming molecules, and external guide sequences.

siRNA is involved in RNA interference (RNAi) which involves a two-step mechanism: an initiation step and an effector step. In the first step, input double-stranded (ds) RNA (siRNA) is processed into small fragments, such as 21-23-nucleotide 'guide sequences'. RNA amplification occurs in whole animals. Typically then, the guide RNAs can be incorporated into a protein RNA complex which is capable of degrading RNA, the nuclease complex, which has been called the RNA-induced silencing complex (RISC). This RISC complex acts in the second effector step to destroy mRNAs that are recognized by the guide RNAs through base-pairing interactions. RNAi involves the introduction by any means of double stranded RNA into the cell which triggers events that cause the degradation of a target RNA. RNAi is a form of post-transcriptional gene silencing. In addition to the siRNAs disclosed herein, disclosed are RNA hairpins that can act in RNAi. For a description of making and using RNAi molecules see, e.g., Hammond et al., Nature Rev Gen 2: 110-119 (2001); Sharp, Genes Dev 15: 485-490 (2001), Waterhouse et al., Proc. Natl. Acad. Sci. USA 95(23): 13959-13964 (1998) all of which are incorporated herein by reference in their entireties and at least form material related to delivery and making of RNAi molecules.

RNAi has been shown to work in many types of cells, including mammalian cells. For work in mammalian cells it is preferred that the RNA molecules which will be used as targeting sequences within the RISC complex are shorter. For example, less than or equal to 50 or 40 or 30 or 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, or 10 nucleotides in length. These RNA molecules can also have overhangs on the 3' or 5' ends relative to the target RNA which is to be cleaved. These overhangs can be at least or less than or equal to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 nucleotides long.

Antisense molecules are designed to interact with a target nucleic acid molecule through either canonical or non-canonical base pairing. The interaction of the antisense molecule and the target molecule is designed to promote the destruction of the target molecule through, for example, RNAseH mediated RNA-DNA hybrid degradation. Alternatively the antisense molecule is designed to interrupt a processing function that normally would take place on the target molecule, such as transcription or replication. Antisense molecules can be designed based on the sequence of the target molecule. Numerous methods for optimization of antisense efficiency by finding the most accessible regions of the target molecule exist. Exemplary methods would be in vitro selection experiments and DNA modification studies using DMS and DEPC. It is preferred that antisense molecules bind the target molecule with a dissociation constant (k_d) less than or equal to 10^{-6}, 10^{-8}, 10^{-10}, or 10^{-12}. A representative sample of methods and techniques which aid in the design and use of antisense molecules can be found in the following non-limiting list of U.S. Pat. Nos. 5,135,917, 5,994,320, 6,046,319, and 6,057,437, all of which are incorporated herein by reference in their entireties.

Aptamers are molecules that interact with a target molecule, preferably in a specific way. Typically aptamers are small nucleic acids ranging from 15-50 bases in length that fold into defined secondary and tertiary structures, such as stem-loops or G-quartets. Aptamers can bind a chemokines and block its function (see, e.g., Marro et al., *Biochem Biophys Res Commun.* 2006 Oct. 13; 349:270-6). Aptamers can bind very tightly with k_ds from the target molecule of less than 10^{-12} M. It is preferred that the aptamers bind the target molecule with a k_d less than 10^{6}, 10^{-8}, 10^{-10}, or 10^{12}. Aptamers can bind the target molecule with a very high degree of specificity. For example, aptamers have been isolated that have greater than a 10000 fold difference in binding affinities between the target molecule and another molecule that differ at only a single position on the molecule (U.S. Pat. No. 5,543,293). It is preferred that the aptamer have a k_d with the target molecule at least 10, 100, 1000, 10,000, or 100,000 fold lower than the k_d with a background binding molecule. Representative examples of how to make and use aptamers to bind a variety of different target molecules can be found in the following non-limiting list of U.S. Pat. Nos. 5,476,766, 5,861,254, 6,030,776, and 6,051,698, all of which are incorporated herein by reference in their entireties.

Ribozymes are nucleic acid molecules that are capable of catalyzing a chemical reaction, either intramolecularly or intermolecularly. Ribozymes are thus catalytic nucleic acid. It is preferred that the ribozymes catalyze intermolecular reactions. There are a number of different types of ribozymes that catalyze nuclease or nucleic acid polymerase type reactions which are based on ribozymes found in natural systems, such as hammerhead ribozymes, (see, e.g., U.S. Pat. Nos. 5,334,711 and 5,861,288, WO 9858058 and WO 9718312) hairpin ribozymes (see, e.g., U.S. Pat. Nos. 5,631,115 and 6,022,962), and tetrahymena ribozymes (see, e.g., U.S. Pat. Nos. 5,595,873 and 5,652,107). There are also a number of ribozymes that are not found in natural systems, but which have been engineered to catalyze specific reactions de novo (see, e.g., U.S. Pat. Nos. 5,580,967 and 5,910,408). Preferred ribozymes cleave RNA or DNA substrates, and more preferably cleave RNA substrates. Ribozymes typically cleave nucleic acid substrates through recognition and binding of the target substrate with subsequent cleavage. This recognition is often based mostly on canonical or non-canonical base pair interactions. This property makes ribozymes particularly good candidates for target specific cleavage of nucleic acids because recognition of the target substrate is based on the target substrates sequence. Representative examples of how to make and use ribozymes to catalyze a variety of different reactions can be found in U.S. Pat. Nos. 5,646,042, 5,869,253, 5,989,906, and 6,017,756, all of which are incorporated herein by reference in their entireties.

Triplex forming functional nucleic acid molecules are molecules that can interact with either double-stranded or single-stranded nucleic acid. When triplex molecules interact with a target region, a structure called a triplex is formed, in which three strands of DNA form a complex dependant on both Watson-Crick and Hoogsteen base-pairing. Triplex molecules are preferred because they can bind target regions with high affinity and specificity. It is preferred that the triplex forming molecules bind the target molecule with a k_d less than 10^{-6}, 10^{-8}, 10^{-10}, or 10^{-12}. Representative examples of how to make and use triplex forming molecules to bind a variety of different target molecules can be found in U.S. Pat. Nos. 5,176,996, 5,683,874, 5,874,566, and 5,962,426, all of which are incorporated herein by reference in their entireties.

External guide sequences (EGSs) are molecules that bind a target nucleic acid molecule forming a complex, and this complex is recognized by RNase P, which cleaves the target molecule. EGSs can be designed to specifically target a RNA molecule of choice. RNAse P aids in processing transfer RNA (tRNA) within a cell. Bacterial RNAse P can be recruited to cleave virtually any RNA sequence by using an EGS that causes the target RNA:EGS complex to mimic the natural tRNA substrate (see, e.g., WO 92/03566 by Yale, and Forster and Altman, *Science* 238:407-409 (1990)).

Similarly, eukaryotic EGS/RNAse P-directed cleavage of RNA can be utilized to cleave desired targets within eukaryotic cells. (Yuan et al., *Proc. Natl. Acad. Sci. USA* 89:8006-8010 (1992); WO 93/22434 by Yale; WO 95/24489 by Yale; Yuan and Altman, *EMBO J.* 14:159-168 (1995), and Carrara et al., *Proc. Natl. Acad. Sci. USA* 92:2627-2631 (1995)). Representative examples of how to make and use EGS molecules to facilitate cleavage of a variety of different target molecules be found in the following non-limiting list of U.S. Pat. Nos. 5,168,053, 5,624,824, 5,683,873, 5,728,521, 5,869,248, and 5,877,162, all of which are incorporated herein by reference in their entireties.

Methods for Prevention or Inhibition of Migration or Metastasis of Cancer Cells Having Elevated Expression of CCL25 and/or CCR9

Another aspect of the present application relates to a method for prevention or inhibition of the migration or metastasis of cancer cells having elevated expression of CCL25 and/or CCR9 in a subject.

In one embodiment, the method comprises the step of administering to the subject a therapeutically effective amount of an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof.

In another embodiment, the method comprises the step of administering to the subject an expression vector that expresses an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof in said subject.

In another embodiment, the method comprises administering to the subject an expression vector that expresses an agent capable of inhibiting the expression of CCL25 or CCR9, or a biological activity of CCL25 or CCR9, or the interaction between CCL25 and CCR9.

In another embodiment, the expression vector is capable of delivering nucleotides encoding CCL25 and/or CCR9 into a target cell to induce the host to produce anti-CCL25 and/or CCR9 antibodies.

Expression of CCL25 and/or CCR9 in cancer cells can be determined using methods well known in the art, such as immunostaining or quantitative PCR. Cancer cells that are known to overexpress CCL25 and/or CCR9 include, but are not limited to, melanoma cells and carcinoma cells. Examples of carcinoma include, but are not limited to, ovarian cancer, vaginal cancer, cervical cancer, uterine cancer, prostate cancer, anal cancer, rectal cancer, colon cancer, stomach cancer, pancreatic cancer, insulinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine tumor, breast cancer, lung cancer, esophageal cancer, oral cancer, brain cancer, medulloblastoma, neuroectodermal tumor, glioma, pituitary cancer, and bone cancer.

In one embodiment, the cancer cells are brain cancer cells. In another embodiment, the cancer cells are bone cancer cells. In another embodiment, the cancer cells are pituitary cancer cells. In yet another embodiment, the cancer cells are ovarian cancer cells.

Method for Enhancing the Effect of Chemotherapy

Another aspect of the present application relates to a method for enhancing the effect of chemotherapy. In one embodiment, the method comprises administering to a subject who is under chemotherapy for a cancer, an effective amount of an anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof.

In another embodiment, the method comprises administering to a subject who is under chemotherapy for a cancer, an effective amount of an expression vector that expresses anti-CCL25 antibody, or an anti-CCR9 antibody, or a combination thereof.

In another embodiment, the method comprises administering to a subject who is under chemotherapy for a cancer an expression vector that expresses an agent capable of inhibiting the expression of CCL25 or CCR9, or a biological activity of CCL25 or CCR9, or the interaction between CCL25 and CCR9. In another embodiment, the expression vector is capable of delivering nucleotides encoding CCL25 and/or CCR9 into a target cell to induce the host to produce anti-CCL25 and/or CCR9 antibodies.

In one embodiment, the subject is under chemotherapy for blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma or genii cell tumor. In another embodiment, the subject is under chemotherapy for brain cancer. In another embodiment, the subject is under chemotherapy for bone cancer. In another embodiment, the subject is under chemotherapy for pituitary cancer. In yet another embodiment, the subject is under chemotherapy for ovarian cancer.

Compositions and Kits for Treating or Preventing Cancer

Another aspect of the present application relates to compositions and kits for treating or preventing cancer. In one embodiment, the composition comprises (1) an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof, and (2) a pharmaceutically acceptable carrier. In another embodiment, the composition comprises (1) an expression vector carrying the coding sequence for an anti-CCL25 antibody, an anti-CCR9 antibody, or a combination thereof, and (2) a pharmaceutically acceptable carrier. In another embodiment, the composition comprises (1) an expression vector carrying the coding sequence for an agent that inhibits the expression of CCL25 or CCR9, or a biological activity of CCL25 or CCR9, or the interaction between CCL25 and CCR9, and (2) a pharmaceutically acceptable carrier.

In one embodiment, said compositions and kits are for treating or preventing blastoma, carcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma or germ cell tumor. In particular embodiments, said carcinoma is selected from the group consisting of ovarian cancer, vaginal cancer, cervical cancer, uterine cancer, prostate cancer, anal cancer, rectal cancer, colon cancer, stomach cancer, pancreatic cancer, insulinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine tumor, breast cancer, lung cancer, esophageal cancer, oral cancer, brain cancer, medulloblastoma, neuroectodermal tumor, glioma, pituitary cancer, and bone cancer.

The composition of the present application may contain a single type of antibody, such as an anti-CCL25 or anti-CCR9 antibody alone, or both types of antibodies. The composition may also contain therapeutically effective amounts of antibodies specific for one or more additional antigens as described above as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect one another. For example, where the carcinoma being treated is ovarian cancer, it may be desirable to prepare a therapeutic formulation comprising anti-CCL25 and/or anti-CCR9 antibodies with one or more further anti-cancer determinant antibodies, such as an anti-CEA, anti-CA125 and/or anti-TA90 in a single formulation. In some embodiments of the present application, a therapeutic antibody may be combined with an chemotherapy agent or a cytotoxic agent. In other embodiments of the present application, a therapeutic antibody may be combined with an anti-inflammatory agent or a thrombolytic agent. Such agents are suitably present in combination in amounts that are effective for the purpose intended.

As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, solubilizers, fillers, stabilizers, binders, absorbents, bases, buffering agents, lubricants, controlled release vehicles, diluents, emulsifying agents, humectants, lubricants, dispersion media, coatings, antibacterial or antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well-known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary agents can also be incorporated into the compositions. In certain embodiments, the pharmaceutically acceptable carrier comprises serum albumin.

The pharmaceutical composition of the application is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intrathecal, intra-arterial, intravenous, intradermal, subcutaneous, oral, transdermal (topical) and transmucosal administration. In certain embodiments, the pharmaceutical composition is administered directly into a tumor tissue.

Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine; propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the injectable composition should be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., anti-CCL25 or anti-CCR9 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active, ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Stertes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the pharmaceutical compositions are formulated into ointments, salves, gels, or creams as generally known in the art.

In certain embodiments, the pharmaceutical composition is formulated for sustained or controlled release of the active ingredient. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially, for example, from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein includes physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the application are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the application, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. In certain embodiments, single dosage contains 0.01 μg to 50 mg of an anti-CCL25 or anti-CCR9 antibody. The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

The present application is further illustrated by the following examples that should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application, as well as the Figures and Tables, are incorporated herein by reference.

EXAMPLE 1

In Vitro Analysis of CCL25 and CCR9Expression and Activity in Various Carcinomas

As shown in FIG. **1**, CCL25 is expressed by breast cancer tissue. Breast cancer tissue was stained with isotype control or anti-CCL25 antibodies. Magenta color shows CCL25 staining. An Aperio ScanScope CS system with a 40× objective captured digital images. A representative case of breast cancer indicated and immuno-intensity of CCL25.

FIG. **2** demonstrates CCL25 inhibition of cisplatin-induced reductions in breast cancer cell line growth is demonstrated. MDA-MB-231 cells were cultured with 0 or 100 ng/ml of CCL25 plus isotype control or anti-CCR9Ab for 24 hours, along with increasing concentrations of cisplatin. Cell proliferation was determined by BrdU incorporation and assays were repeated 3 times and performed in triplicate. Asterisks indicate statistical significant differences ($p<0.01$) between CCL25-treated and untreated BrCa cells.

FIGS. **3**A-B show that CCL25 protects breast cancer cells from cisplatin-induced apoptosis. MDA-MB-231 cells were cultured for 24 hours with 5 mg/ml of cisplatin alone or with 0 or 100 ng/ml CCL25 plus 1 mg/ml of anti-human CCR9 or isotype controls (A). Cells were harvested and stained with annexin V and propidium iodide (PI). Analysis by flow cytometry of the stained cells distinguished apoptotic (annexin V positive) cells from viable (no fluorescence) and necrotic (PI positive) cells. Asterisks indicate statistical significant differences ($p<0.01$) between CCL25-treated and untreated breast cancer cells. MDA-MB-231 cell line was cultured for 24 hours with 5 mg/ml cisplatin or with 0 or 100 ng/ml of CCL25 plus 1 mg/ml or anti-human CCR9 or isotype control Abs (B). Detection of apoptotic cells was carried out using the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) method. Apoptotic cells exhibited nuclear green fluorescence with a standard fluorescence filter set (520±20 nm). Asterisks indicate statistical significant differences ($p<0.01$) between cisplatin CCL25-treated and untreated breast cancer cell line.

FIGS. **4**A-B show PI3K and Akt activation by CCL25-CCR9 interactions in a breast cancer cell line. MDA-MB-231 cells were tested for their ability to activate PI3K and Akt following treatment with CCL25, cisplatin and specific kinase inhibitors (wortmannin and PF-573,228). In situ total and phosphorylated PI3K and Akt levels were quantified by Fast Activated Cell-based ELISA before (0 minutes) or after (5 or 10 minutes) CCL25 stimulation in the presence of cisplatin and kinase inhibitors. The ratio±SEM of active (phosphorylated) to total PI3K (A) or Akt (B) are presented in from 3 separate experiments performed in triplicate. Asterisks indicate statistical differences between untreated and CCL25-treated cells and CCL25+cisplatin-treated cells.

FIGS. **5**A-B show GSK-3β and FKHR phosphorylation following CCL25 treatment of a breast cancer cell line. MDA-MB-231 cells were tested for their ability to phosphorylate GSK-3b and FKHR following treatment with CCL25, cisplatin and specific-kinase inhibitors (wortmannin and PF-573,228). In situ total and phosphorylated GSK-3β and FKHR levels were quantified by Fast Activated Cell-based ELISA before (0 minutes) or after (5 or 10 minutes) CCL25 stimulation in the presence of cisplatin and kinase inhibitors. The ratio of phosphorylated to total GSK-3β (A) or FKHR (B) are presented in ±SE from 3 separate experiments performed in triplicate. Asterisks indicate statistical differences ($p<0.01$) between untreated and CCL25-treated cells and CCL25+cisplatin-treated cells.

FIG. **6** shows CCR9 and CCL25 expression by ovarian cancer tissues. Ovarian cancer tissues from non-neoplastic (n=8), serous adenocarcinoma (n=9), serous papillary cystadenoma (n=1), endometrioid adenocarcinoma (n=5), mucinous adenocarcinoma (n=2), Cystadenoma (n=3), mucinous boderline adenocarcinoma (n=1), clear cell carcinoma (n=5), granulosa cell tumor (n=3), dysgerminoma (n=3), transitional cell carcinoma (n=3), Brenner tumor (n=1), yolk sac tumor (n=4), adenocarcinoma (n=1) and fibroma (n=2) were stained with isotype control or anti-CCR9 and CCL25 antibodies. Brown (DAB) color shows CCR9 staining and

Magenta color show CCL25. An Aperio ScanScope CS system with a 40× objective captured digital images of each slide. Representative cases show immunointensities of CCR9 and CCL25.

FIGS. **7**A-B show an analysis of CCL25 expression by ovarian cancer tissues. CCL25 expression were analyzed and presented by modified box plot (A). Lower, middle and upper lines, respectively, in the box represent the first quartile (Q1), Median (Q2) and third quartile (Q3). Upper and lower whiskers represent the median±1.5 (Q3-Q1). Significant differences from non-neoplastic are indicated in the lower panel. The table (B) shows respective p values or significant differences between non-neoplastic tissue (NN) and serous adenocarcinoma (SA), endometrioid adenocarcinoma (EC), mucinous adenocarcinoma (MA), cystadenoma (C), mucinous boderline adenocarcinoma (MBA), clear cell carcinoma (CCC), granulosa cell tumor (GCT), dysgerminoma (D), transitional cell carcinoma (TCC), Brenner tumor (BT), yolk sac tumor (YST), adenocarcinoma (A), and fibroma (F).

FIGS. **8**A-B show an analysis of CCR9 expression by ovarian cancer tissues. CCR9 expression was analyzed and presented by modified box plot (A). Lower, middle and upper lines, respectively, in the box represent the first quartile (Q1), Median (Q2) and third quartile (Q3). Upper and lower whiskers represent the median±1.5 (Q3-Q1 significant differences from non-neoplastic are indicated in the lower panel. The table (B) shows respective p values or significant differences between non-neoplastic tissue (NN) and serous adenocarcinoma (SA), endometrioid adenocarcinoma (EC), mucinous adenocarcinoma (MA), cystadenoma (C), mucinous boderline adenocarcinoma (MBA), clear cell carcinoma (CCC), granulosa cell tumor (GCT), dysgerminoma (D), transitional cell carcinoma (TCC), Brenner tumor (BT), yolk sac tumor (YST), adenocarcinoma (A), and fibroma (F).

FIGS. **9**A-B show CCR9 and CCL25 expression by ovarian cancer cell lines. Ovarian cancer cells were stained with fluorescein (FITC)-conjugated anti-CCR9 or FITC-conjugated isotype control antibody and analyzed by FACS (A). Ovarian cancer cells were stained with FITC-conjugated anti-CCR9, intracellular CCL25 was stained with phycoerythrin (PE)-conjugated anti-CCL25 antibody and nuclei were stained with Draq-5 (B). Merged data show the expression of CCR9 on the surface and CCL25 expression in the nucleus.

FIGS. **10**A-B show hypoxia-regulated CCR9 mRNA and surface protein expression by ovarian cancer cells. Total RNA was isolated from SKOV-3 cell line under normoxic and hypoxic conditions or from normal primary ovary tissue. Quantitative RT-PCR analysis of CCR9 mRNA expression was performed in triplicate. The copies of transcripts are expressed relative to actual copies of 18S rRNA+SE (A). SKOV-3 cells under normoxia and hypoxia were stained with PE-conjugated isotype control antibody (Ab) (solid histogram) or PE-conjugated anti-CCR9 monoclonal Ab (open histogram) and quantified by flow cytometry (B). The mean fluorescent intensities of PE-positive cells are shown. Symbols indicate statistical significant ($p<0.01$) differences in CCR9 expression between normal tissue or isotype control and OvCa cells (@) or between normoxic and hypoxic cells (*).

FIGS. **11**A-B show hypoxia-mediated and CCL25-mediated migration and invasion of SKOV-3 cells. SKOV-3 cells were tested for their ability to migrate toward chemotactic gradients of CCL25 (A). Cells were co-cultured with 1.0 μg/ml mouse anti-CCR9 antibody (Ab) or isotype control Ab during migration assays using 100 ng/ml of CCL25 under normoxic or hypoxic conditions. Also, SKOV-3 cells were tested for their ability to invade or translocate cross Matrigel™ matrix in response to 100 ng/ml of CCL25 under hypoxic or normoxic conditions (B). Cells were co-cultured with 1.0 μg/ml monoclonal antibodies against CCR9 during invasion assays using 100 ng/ml of CCL25 under normoxic or hypoxic conditions. The number of cells (+SE) that migrated or invaded is shown with symbols that indicate significant ($p<0.01$) differences between CCL25-treated and untreated normoxic cells (#), CCL25-treated and untreated hypoxic cells (@), or similarly treated normoxic and hypoxic cells (*).

FIGS. **12**A-B show CCL25-induced collagenase expression by SKOV-3 cells. Cells were tested for their ability to express collagenases (MMP-1, MMP-8, and MMP-13) mRNA and active protein. SKOV-3 cells were cultured for 24 hours alone, with 100 ng/ml of CCL25+1 μg/ml of isotype control antibody (Ab), or CCL25+1 μg/ml of mouse anti-CCR9 Ab under normoxic or hypoxic conditions. Total RNA was isolated and quantitative RT-PCR analysis was performed for mRNA expression of collagenases and transcript copies are presented relative to actual copies of 18S rRNA (A). Active collagenases were quantified by Fluorokine and Biotrak assays in conditioned media (B). Symbols indicate significant ($p<0.01$) differences between CCL25-treated and untreated normoxic cells (#), CCL25-treated and untreated hypoxic cells (@), or similarly treated normoxic and hypoxic cells (*).

FIGS. **13**A-B show CCL25-induced gelatinase expression by SKOV-3 cells. Cells were tested for their ability to express gelatinases (MMP-2 and MMP-9) mRNA and active protein. SKOV-3 cells were cultured for 24 hours alone, with 100 ng/ml of CCL25+1 μg/ml of isotype control antibody (Ab), or CCL25+1 μg/ml of mouse anti-CCR9Ab under normoxic or hypoxic conditions. Total RNA was isolated and quantitative RT-PCR analysis was performed for mRNA expression of gelatinases and transcript copies are presented relative to actual copies of 18S rRNA (A). Active gelatinases in conditioned media were quantified by Fluorokine and Biotrak assays (B). Symbols indicate significant ($p<0.01$) differences between CCL25-treated and untreated normoxic cells (#), CCL25-treated and untreated hypoxic cells (@), or similarly treated normoxic and hypoxic cells (*).

FIGS. **14**A-B show CCL25-induced stromelysin expression by SKOV-3 cells. Cells were tested for their ability to express stromelysins (MMP-3, MMP-10, and MMP-11) mRNA and active protein. SKOV-3 cells were cultured for 24 hours alone, with 100 ng/ml of CCL25+1 μg/ml of isotype control antibody (Ab), or CCL25+1 μg/ml of mouse anti-CCR9 Ab under normoxic or hypoxic conditions. Total RNA was isolated and quantitative RT-PCR analysis was performed for mRNA expression of stromelysins and transcript copies are presented relative to actual copies of 18S rRNA (A). Active stromelysins were quantified by Fluorokine and Biotrak assays in conditioned media (B). Symbols indicate significant ($p<0.01$) differences between CCL25-treated and untreated normoxic cells (#), CCL25-treated and untreated hypoxic cells (@), or similarly treated normoxic and hypoxic cells (*).

FIG. **15** shows CCR9 expression by prostate cancer cell lines. Prostate cancer cell lines (C4-2B, LNCaP, and PC3) and normal prostate cells (RWPE-1) were stained with FITC-conjugated anti-human CCR9 (green) and 7AAD (nuclear stain; red). Positively stained cells were imaged and quantified by Amnis ImageStream. Panels on the right show the mean fluorescence intensity of CCR9 staining.

FIGS. **16**A-D show CCR9 expression by prostate tissue. Tissue microarrays (TMA) were obtained from the National Institutes of Health (NIH), National Cancer Institute (NCI) and the University of Alabama at Birmingham and stained for

CCR9. Aperio Scan Scope system with a 40× objective captured digital images of each slide. Representative cases of prostate cancer (CaP)(A), matched benign prostate tissue (MB)(B) and negative controls are indicated and intensities of CCR9 for all tissues scanned and analyzed were quantified using ImageScope software (v.6.25). FIG. **27**D shows the CCR9 immunointensity between MB, benign prostatic hyperplasia (BPH), and prostate cancer (PCa). Asterisks indicate significant ($p<0.01$) differences in CCR9 immunointensity between MB, BPH, and PCa tissue.

FIGS. **17**A-D show CCL25 expression by prostate cancer tissue. Neuroendocrine differentiation of endocrine-paracrine cell phenotypes frequently occurs in prostatic malignancies and has potential prognostic and therapeutic implications. Paracrine cell phenotypes can be considered to be an androgen-insensitive, post-mitotic subpopulation in the prostate and prostate cancer. FIG. **17**A demonstrates the expression of CCL25 in paracrine pattern within prostate interepithelial neoplasia. The double-headed arrow points to multiple paracrine cells producing CCL25 (red); brown arrow points cells expressing CCR9 (Brown). FIG. **17**B shown cell stained red for CCL25. Brown arrow points the cell NSE. FIGS. **17**A and C are higher magnifications of FIGS. **17**D and B, respectively.

FIG. **18** shows serum CCL25 levels in normal healthy donors or patients with prostatic disease. ELISA was used to quantify CCL25 in serum from normal healthy donors, prostate cancer (PCa), prostate interepithelial neoplasia (PIN), and benign prostate hyperplasia (BPH). Asterisks indicate significant differences ($p<0.05$) of CCL25 levels compared to normal healthy donors.

FIGS. **19**A-C shows CCL25 expression by mouse bone marrow cells. Bone marrow cells from non-tumor bearing (A) and tumor-bearing (B) mice were aspirated and stained with FITC-conjugated anti-CCL25 antibody. Positively stained cells (C) were quantified by Amnis ImageStream. Image-based analysis was performed using IDEAS-software and indicated a 1.6 fold increase in CCL25 expression by bone marrow cells after prostate tumor challenge.

FIGS. **20**A-B show CCR9-mediated prostate cancer cell migration (A) and invasion (B). LNCaP, PC3, and C4-2b cells were tested for their ability to migrate to no additions (open bar), 100 ng/mL of CCL25 (hashed bar), or 100 ng/mL of CCL25+1 μg/mL anti-CCL25 antibody (solid bar). The number of cells (±SEM) that migrated and invaded in response to CCL25 from the initial 104 cells used to seed the migration and invasion chamber, show migration was CCL25 dependent and inhibited by anti-CCL25 antibody blockade. Asterisks indicate significant differences ($p<0.01$) between no additions and CCL25-treated cells.

FIG. **21** shows CCL25-induced active matrix metalloproteinase (MMP) expression by LNCaP, PC3, and C4-2b prostate cancer cell lines. Cells were cultured for 24 hours without (open boxes) or with 100 ng/mL CCL25 (solid boxes). MMP-1, MMP-2, MMP-3, MMP-9, MMP-10, and MMP-11 protein levels, in cultured supernatants, were determined by MMP activity assays. Asterisks show a significant ($P<0.05$) increase or decrease in MMP secretion by a CCL25-treated cell line compared with the untreated cell line.

FIGS. **22**A-F show inhibition of bone metastasis of PC3 prostate cancer cell line by CCR9 knockdown. Mice were challenged with a luciferase- and doxycyclene-inducible CCR9-specific shRNA-expressing PC3 cell line (A, D). Mice were challenged with this cell line by intracardiac injection. Subsequently, mice received no additions or doxycycline (0.2 mg/mL) in drinking for 21 days. Metastasis and tumor growth was monitored every week by Caliper Xenogen 100 in vivo imaging system. There were no changes 24 hours post challenge (B, E), but three weeks after challenge significantly less CCR9 knockdown PC3 (F) cells grew as bone metastases than compared to CCR9-positive PC3 cells (C).

FIG. **23** shows serum CCL25 levels in lung cancer patients. CCL25 ELISAs were performed to quantify CCL25 levels in serum from patients diagnosed with adenocarcinoma (Adeno Ca; n=14), squamous cell carcinoma (SSC; n=17), and normal healthy donors (control; n=9). ELISAs were capable of detecting >5 pg/mL of CCL25. Solid circles indicate individual serum CCL25 levels and lines show median concentrations of each group. Asterisks indicate significant differences ($p<0.01$) between controls and groups with lung cancer.

FIGS. **24**A-C show CCR9 expression by non-neoplastic lung and lung cancer tissues. Lung tissues from non-neoplastic (n=8) (A), adenocarcinoma (n=54) (B), and squamous cell carcinoma (n=24) (C) were stained with isotype control or anti-CCR9 antibodies. Brown (DAB) color show CCR9 staining.

FIGS. **25**A-C show CCR9-CCL25 expression by colon cancer tissues. Colon tissues from non-neoplastic (n=8) and adenocarcinoma (n=16) were stained with isotype control (A), anti-CCR9 (B) or anti-CCL25 (C) antibodies. Brown (DAB) stain indicates CCR9 positivity and magenta stain show CCL25 positivity.

EXAMPLE 2

Detecting Chemokine Expression Levels with Real Time-PCR Analysis

Primer Design

Messenger RNA sequences for CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR5a, CXCR5b, CXCR6, CXCR7, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL24, CCL25, CCL25-1, CCL25-2, CCL27, CCL28, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, XCL1, XCL2, XCR1, CX3CR1, or CX3CL1 were obtained from the NIH-NCBI gene bank database. Primers were designed using the BeaconJ 2.0 computer program. Thermodynamic analysis of the primers was conducted using computer programs: Primer Premier) and MIT Primer 3. The resulting primer sets were compared against the entire human genome to confirm specificity.

Real Time PCR Analysis

Cancer cell lines (ATCC, Rockville, Md.) were cultured in RMPI-1640 containing 10% fetal calf serum supplemented with non-essential amino acids, L-glutamate, and sodium pyruvate (complete media). Primary tumor and normal-paired matched tissues were obtained from clinical isolates (Clinomics Biosciences, Frederick, Md. and UAB Tissue Procurement, Birmingham, Ala.). Messenger RNA (mRNA) was isolated from 106 cells using TriReagent (Molecular Research Center, Cincinnati, Ohio) according to manufacturer's protocols. Potential genomic DNA contamination was removed from these samples by treatment with 10 U/Fl of RNase free DNase (Invitrogen, San Diego, Calif.) for 15 minutes at 37° C. RNA was then precipitated and resuspended in RNA Secure (Ambion, Austin, Tex.). The cDNA was generated by reverse transcribing approximately 2 μg of total RNA using Taqman7 reverse transcription reagents (Applied Biosystems, Foster City, Calif.) according to manufacturer's protocols. Subsequently, cDNAs were amplified with specific human cDNA primers, to CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR5a, CXCR5b, CXCR6, CXCR7, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL24, CCL25, CCL25-1, CCL25-2, CCL27, CCL28, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11, XCL1, XCL2, XCR1, CX3CR1 or CX3CL1, using SYBR7Green PCR master mix reagents (Applied Biosystems) according to manufacturer's protocol. The level of copies of mRNA of these targets were evaluated by real-time PCR analysis using the BioRad Icycler and software (Hercules, Calif.).

The RT-PCR products obtained using CXCL1-, CXCL2-, CXCL3-, CXCL4-, CXCL5-, CXCL6-, CXCL7-, CXCL8-, CXCL9-, CXCL10-, CXCL11-, CXCL12-, CXCL13-, CXCL14-, CXCL15-, CXCL16-, CXCR1-, CXCR2-, CXCR3-, CXCR4-, CXCR5-, CXCR5a-, CXCR5b-, CXCR6-, CXCR7-, CCL1-, CCL2-, CCL3-, CCL4-, CCL5-, CCL6-, CCL7-, CCL8-, CCL9-, CCL10-, CCL11-, CCL12-, CCL13-, CCL14-, CCL15-, CCL16-, CCL17-, CCL18-, CCL19-, CCL20-, CCL21-, CCL22-, CCL24-, CCL25-, CCL25-1-, CCL25-2-, CCL27-, CCL28-, CCR1-, CCR2-, CCR3-, CCR4-, CCR5-, CCR6-, CCR7-, CCR8-, CCR9-, CCR10-, CCR11-, XCL1-, XCL2-, XCR1-, CX3CR1-, or CX3CL1-specific primer sets did not cross react with other gene targets due to exclusion of primers that annealed to host sequences (NIH-NCBI Genebank). The primers produced different size amplicon products relative the polymorphisms that resulted in CXCR5a versus CXCR5b and CCL25, CCL25-1, versus CCL25-2. To this end, RT-PCR analysis of adenoma, carcinoma, leukemia, lymphoma, melanoma, and/or myeloma cell lines and tumor tissue revealed that chemokines and chemokine receptors were differentially expressed by cancer cells.

EXAMPLE 3

Anti-Chemokine and Anti-Chemokine Receptor Antibodies Inhibit Tumor Cell Growth In Vitro and In Vivo

Anti-Sera Preparation

15 amino acid peptides from CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCL12, CXCR5a, CXCR5b, CXCL13, CXCR6, CXCL16, CCL16, CCL25, CCL25-1, CCL25-2, CCR9, CX3CR1, and CX3CL1 (SEQ ID NOS:1-21) were synthesized (Sigma Genosys, The Woodlands, Tex.) and conjugated to hen egg lysozyme (Pierce, Rockford, Ill.) to generate the antigen for subsequent immunizations for anti-sera preparation or monoclonal antibody generation. The endotoxin levels of chemokine peptide conjugates were quantified by the chromogenic *Limulus amebocyte* lysate assay (Cape Cod, Inc., Falmouth, Miss.) and shown to be <5 EU/mg. 100 μg of the antigen was used as the immunogen together with complete Freund's adjuvant Ribi Adjuvant system (RAS) for the first immunization in a final volume of 1.0 ml. This mixture was administered in 100 ml aliquots on two sites of the back of the rabbit subcutaneously and 400 ml intramuscularly in each hind leg muscle. Three to four weeks later, rabbits received 100 μg of the antigen in addition to incomplete Freund's adjuvant for 3 subsequent immunizations. Anti-sera were collected when anti-CXCR1, -CXCR2, -CXCL1, -CXCL2, -CXCL3, -CXCL5, -CXCL6-CXCL7, -CXCL8, -CXCL12, -CXCR5a, -CXCR5b, -CXCL13, -CXCR6, -CXCL16, -CCL16, -CCL25, -CCL25-1, -CCL25-2, -CCR9, -CX3CR1, and -CX3CL1 antibody titers reached 1:1,000,000. Subsequently, normal or anti-sera were heat-inactivated and diluted 1:50 in PBS.

Monoclonal Antibody Preparation

15 amino acid peptides from CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCL12, CXCR5a, CXCR5b, CXCL13, CXCR6, CXCL16, CCL16, CCL25, CCL25-1, CCL25-2, CCR9, CX3CR1, and CX3CL1 were synthesized (Sigma Genosys) and conjugated to hen egg lysozyme (Pierce) to generate the "antigen" for subsequent immunizations for anti-sera preparation or monoclonal antibody generation. The endotoxin levels of chemokine peptide conjugates were quantified by the chromogenic *Limulus amebocyte* lysate assay (Cape Cod, Inc., Falmouth, Miss.) and shown to be <5 EU/mg. 100 μg of the antigen was used as the immunogen together with complete Freund's adjuvant Ribi Adjuvant system (RAS) for the first immunization in a final volume of 200 μl. This mixture was subcutaneously administered in 100 μl aliquots at two sites of the back of a rat, mouse, or immunoglobulin-humanized mouse. Two weeks later, animals received 100 μg of the antigen in addition to incomplete Freund's adjuvant for 3 subsequent immunizations. Serum were collected and when anti-CXCR1, -CXCR2, -CXCL1, -CXCL2, -CXCL3, -CXCL5, -CXCL6-CXCL7, -CXCL8, -CXCL12, -CXCR5a, -CXCR5b, -CXCL13, -CXCR6, -CXCL16, -CCL16, -CCL25, -CCL25-1, -CCL25-2, -CCR9, -CX3CR1, or -CX3CL1 antibody titers reached 1:2,000,000, hosts were sacrificed and splenocytes were isolated for hybridoma generation. Briefly, B cells from the spleen or lymph nodes of immunized hosts were fused with immortal myeloma cell lines (e.g., YB2/0). Hybridomas were next isolated after selective culturing conditions (i.e., HAT-supplemented media) and limiting dilution methods of hybridoma cloning. Cells that produce antibodies with the desired specificity were selected using ELISA. Hybridomas from normal rats or mice were humanized with molecular biological techniques in common use. After cloning a high affinity and prolific hybridoma, antibodies were isolated from ascites or culture supernatants and adjusted to a titer of 1:2,000,000 and diluted 1:50 in PBS.

Anti-Sera or Monoclonal Antibody Treatment

Immunodeficient nude NIH-III mice (8 to 12 weeks old, Charles River Laboratory, Wilmington, Mass.), which lack T, B, and NK cells, received 1×10^6 cancer cells, subcutaneously, for the establishment of a tumor. The established solid tumor was then removed from the host for immediate implantation or stored in liquid nitrogen for later implantation. Freshly isolated or liquid nitrogen frozen tumor tissue (1 g) were surgically implanted in the intestinal adipose tissue for the generation of tumor. Once the xenografted tumor growth reached 5 mm in size, the NIH-III mice received 200 μl intraperitoneal injections of either anti-sera or monoclonal antibodies every three days and the tumor was monitored for progression or regression of growth.

Data Analysis

SigmaStat 2000 (Chicago, Ill.) software was used to analyze and confirm the statistical significance of data. The data were subsequently analyzed by the Student's t-test, using a two-factor, unpaired test. In this analysis, treated samples were compared to untreated controls. The significance level was set at $p<0.05$.

In Vitro Growth Studies

The adenoma, carcinoma, leukemia, lymphoma, melanoma, and/or myeloma cell lines were grown in complete media in the presence or absence of antibodies specific for CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6 CXCL7, CXCL8, CXCR4, CXCL12, CXCR5a, CXCR5b, CXCL13, CXCR6, CXCL16, CCL16, CCR9, CCL25, CCL25-1, CCL25-2, CX3CR1, or CX3CL1. The growth of cancer cell lines expressing CXCR1 and/or CXCR2 were inhibited by antibodies to CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, or CXCL8. Similarly, the growth of cancer cell lines expressing CXCR4 were inhibited by antibodies to CXCR4 or CXCL12. The growth of cancer cell lines expressing CXCR5a or CXCR5a were inhibited by antibodies to CXCR5a, CXCR5b, or CXCL13. The proliferation of cancer cell lines expressing CXCR6 were inhibited by antibodies to CXCR6 or CXCL16. The growth of cancer cell lines expressing CCR9 were inhibited by antibodies to CCR9, CCL25, CCL25-1, or CCL25-2. The propagation of cancer cell lines expressing CX3CR1 were inhibited by antibodies to CX3CR1 or CXC3L1. Of interest, antibodies against the soluble ligands, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCL12, CXCL13, CXCL16, CCL16, CCL25, CCL25-1, CCL25-2, or CX3CL1, were more effective at growth inhibition that those directed against the membrane receptors.

In Vitro Angiogenesis Studies

Microvascular endothelial cells (Cell Systems, Kirkland, Wash.) were grown according to supplier's protocols and allowed to form microvascular venules in an in vitro assay for angiogenesis (BD-Biocoat, Hercules, Calif.), in the presence or absence of antibodies specific for CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCR4, CXCL12, CXCR5a, CXCR5b, CXCL13, CXCR6, CXCL16, CCL16, CCR9, CCL25, CCL25-1, CCL25-2, CX3CR1, or CX3CL1. The angiogenesis was inhibited by antibodies against CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCR4, CXCL12, CXCR6 or CXCL16.

In Vivo Growth Studies

Cancer cell lines or primary tumor tissue were adoptively transferred into NIH-III mice and allowed to form the xenograft tumor of interest. Antibodies directed against CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCR4, CXCL12, CXCR5a, CXCR5b, CXCL13, CXCR6, CXCL16, CCL16, CCR9, CCL25, CCL25-1, CCL25-2; CX3CR1, or CX3CL1 differentially affected the progression and regression of tumor size. In certain cases, antibodies directed towards CXCR1, CXCR2, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCR4, CXCL12, CXCR6 or CXCL16 effectively lead to both regression and impeding progression of tumor growth. Antibodies directed against CXCR4, CXCL12, CXCR5a, CXCR5b, CXCL13, CCL16, CCR9, CCL25, CCL25-1, CCL25-2, CX3CR1, or CX3CL1 were effective at inhibiting the progression of tumor size.

The protein sequences of the chemokines used herein are recorded in NIH-NCBI GenBank as: (1) CXCR1 (ACCESSION #NP 000625), SEQ ID NO:1, (2) CXCR2 (ACCESSION #NP 001548), SEQ ID NO:2, (3) CXCL1 (ACCESSION #NP 001502), SEQ ID NO:3, (4) CXCL2 (ACCESSION #NP 002080), SEQ ID NO:4, (5) CXCL3 (ACCESSION #NP 002081), SEQ ID NO:5, (6) CXCL5 (ACCESSION #NP 002985), SEQ ID NO:6, (7) CXCL6 (ACCESSION #NP 002984), SEQ ID NO:7, (8) CXCL7 (ACCESSION #NP 002695), SEQ ID NO:8, (9) CXCL8 (IL-8, ACCESSION #NP 000575), SEQ ID NO:9, (10) CXCR4 (ACCESSION #NP 003458), SEQ ID NO:10, (11) CXCL12 (ACCESSION #NP 000600), SEQ ID NO:11, (12) CXCR5A (ACCESSION #NP 116743), SEQ ID NO:12, (13) CXCR5B (ACCESSION #NP 001707), SEQ ID NO:13, (14) CXCL13 (ACCESSION #NP 006410), SEQ ID NO:14, (15) CXCR6 (ACCESSION #NP 006555), SEQ ID NO:15, (16) CXCL16 (ACCESSION #NP 071342), SEQ ID NO:16, (17) CCL16 (ACCESSION #NP 004581), SEQ ID NO:17, (18) CCL25 (ACCESSION #NP-005615.2), SEQ ID NO:18, (19) CCL25-1 (ACCESSION #NP 005615), SEQ ID NO:19, (20) CCL25-2 (ACCESSION #NP 683686), SEQ ID NO:20, (21) CX3CR1 (ACCESSION #NP 001328), SEQ ID NO:21, and (22) CX3CL1 (ACCESSION #NP 002987), SEQ ID NO:22.

The cDNA sequences are known and are available in NIH-NCBI GenBank under the following accession numbers: (23) CXCR1 (ACCESSION #NM 000634), SEQ ID NO:23, (24) CXCR2(ACCESSION #NM 001557), SEQ ID NO:24, (25) CXCL1 (ACCESSION #NM 001511), SEQ ID NO:25, (26) CXCL2 (ACCESSION #NM 002089), SEQ ID NO:26, (27) CXCL3 (ACCESSION #NM 002090), SEQ ID NO:27, (28) CXCL5 (ACCESSION #NM 002994), SEQ ID NO:28, (29) CXCL6 (ACCESSION #NM 002993), SEQ ID NO:29, (30) CXCL7 (ACCESSION #NM 002704), SEQ ID NO:30, (31) CXCL8 (IL-8, ACCESSION #NM 000584), SEQ ID NO:31, (32) CXCR4 (ACCESSION #NM 003467), SEQ ID NO:32, (33) CXCL12 (ACCESSION #NM 000609), SEQ ID NO:33, (34) CXCR5A (ACCESSION #NM 032966), SEQ ID NO:34, (35) CXCR5B (ACCESSION #NM 001716), SEQ ID NO:35, (36) CXCL13 (ACCESSION #NM 006419), SEQ ID NO:36, (37) CXCR6 (ACCESSION #NM 006564), SEQ ID NO:37, (38) CXCL16 (ACCESSION #NM 022059), SEQ ID NO:38, (39) CCL16 (ACCESSION #NM 004590), SEQ ID NO:39, (40) CCL25 (ACCESSION #NM_005624.3), SEQ ID NO:40, (41) CCL25-1 (ACCESSION #NM 005624), SEQ ID NO:41, (42) CCL25-2 (ACCESSION #NM 148888), SEQ ID NO:42, (43) CX3CR1 (ACCESSION #NM 001337), SEQ ID NO:43, and (44) CX3CL1 (ACCESSION #NM 002996), SEQ ID NO:44.

As shown in the table below, the particular chemokines which are most which any tumor expresses may vary. The methods of the present application may be customized for a particular patient, depending on the chemokines over-expressed by the patient's own tumor. It is possible to identify the particular chemokines which are over-expressed in the tumor using methods of the application and administer antibodies against that over-expressed chemokine. The tailoring of treatment for the cancer patient is novel, and is a particularly valuable aspect of the application.

Table 1 indicates the differing amounts of particular chemokines over-expressed in particular tumors that were studied.

TABLE 1

Chemokine, Chemokine Receptor and Cancer Association (dependent on stage of disease).

Cancer	Chemokine	Chemokine Receptor
Carcinoma	CCL1, CCL2, CCL4, CCL17, CCL19, CCL21, CCL22, CCL25	CCR2, CCR7, CCR8, CCR9
	CXCL12, CXCL13, CXCL16 CX3CL1	CXCR4, CXCR5, CXCR6 CX3CR1
Leukemia	CCL1, CCL4, CCL17, CCL19, CCL21, CCL22, CCL25	CCR7, CCR8, CCR9
	CXCL12	CXCR4, CXCR7

TABLE 1-continued

Chemokine, Chemokine Receptor and Cancer Association (dependent on stage of disease).

Cancer	Chemokine	Chemokine Receptor
Lymphoma	CXCL12, CXCL13	CXCR4, CXCR5
Melanoma	CCL25, CCL27	CCR9, CCR10
	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, CXCL12, CXCL13, CXCL16	CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7
	CX3CL1	CX3CR1
Sarcoma	CCL1, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL17, CCL22, CCL24	CCR3, CCR5, CCR8
	CXCL12	CXCR4, CXCR7
	CX3CL1	CX3CR1

EXAMPLE 4

CCR9-CCL25 Induced Anti-Apoptotic and/or Survival Signal Involved in PCa Chemo Resistance

LNCaP (hormone responsive, wild type p53 expression), PC3 (hormone refractory, p53 null), and DU145 (hormone refractory, p53 mutated) cell lines are grown with or without CCL25 and with or without doxorubicin (1 μM/2 μM/4 μM), etoposide (20 μM/40 μM), estramustine (4 μM/10 μM), or docetaxel (10 nM/20 nM/40 nM) for 4, 8, 12, and 24 hours. Expression and activation of cell survival, pro- and anti-apoptotic signals (Akt, Src, CamKII, FAK, FKHR, FOXO, CREB, NF-κB, Myc, Fos, Jun Apaf1, Bax, Bcl2, $BclX_L$, BaK, Bad, Bik, Bim, TP53, Caspase-3, -6, -8, -9, survivin, vitronectin, β-Catenin) and molecules responsible for drug resistance or metabolism (Twist-1, Snail-1, Glutathione-S-transferase-π (GST-π), p53, topoisomerase I, IIα, IIβ, and ABC drug transporters) are accessed by real-time PCR and western blot. Briefly, after treatment of cells, changes in the gene expression is tested using real-time PCR. Activation of signaling molecules is also be tested by phosphorylation specific antibody (i.e., Western blot analysis). To further confirm the role of the activated signaling molecules, following CCL25 treatment, expression or activity of the candidate molecules is inhibited using chemical inhibitors or siRNAs and target genes are analyzed by real-time PCR and Western blot analysis. Subsequently, the response of treated cells to chemotherapeutic drugs is evaluated by Vybrant apoptosis assay (Molecular probes) kit.

RNA Isolation and Real-Time PCR

Total RNA is isolated by Trizol™ (Invitrogen) method and quantified by UV spectrophotometry. Quality of RNA is analyzed by electrophoresis. The cDNA synthesis is completed using the iScript™ cDNA synthesis kit (BioRad) as described by the manufacturer. Real-time PCR is performed using IQ™ SYBR green supermix (BioRad) as described by manufacturer and specific primers designed against FAK, FKHR, FOXO, Apaf1, Bax, Bcl2, $BclX_L$, BaK, Bad, Bid, XIAP, Bik, Bim, TP53, cytochrome C, Caspase-3, -6, -8, -9, survivin, lamin, CamKII, vitronectin, β-Catenin, cadherins, Twist-1, Snail-1, CREB, NF-κB, Myc, Fos, Jun, β-actin and GAPDH. The results are calculated by delta Ct to quantify fold changes in mRNAs compared to untreated groups.

Western Blotting

Cells are harvested and resuspended in lysis buffer to extract total protein. Lysis buffer contains 50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% Triton X-100, 1% deoxycholate, 0.1% SDS, 5 mM EDTA supplemented with protease inhibitors, 1 mM phenylmethylsulphonylfluoride, 1 mM benzamidine, 10 μg/mL soybean trypsin inhibitor, 50 μg/mL leupeptin, 1 μg/mL pepstatin and 20 μg/mL aprotinin. Cell lysates are stored on ice for 30 min, centrifuged (14000×g) for 20 min at 4° C., and supernatant is used for western blot analysis of genes demonstrating significant modulation in mRNA level. Similarly, phosphor-specific antibodies are used to test changes in the level of phosphorylation of Akt1/2/3, mTOR, FAK, FKHR, FOXO, and GSK-3P. Moreover, activation of caspases and PARP, following cleavage are evaluated using specific antibodies. The results obtained after chemiluminescent detection of protein bands by ECL plus reagent (Pharmecia) on X-ray film is normalized to β-actin and/or GAPDH using Image J image analysis software (NIH).

Detection of Cytochrome C Release

Cells are collected and washed in PBS, and resuspended in extraction buffer containing 220 mM mannitol, 68 mM sucrose, 50 mM PIPES-KOH, pH 7.4, 50 mM KCl, 5 mM EGTA, 2 mM $MgCl_2$, 1 mM DTT, and protease inhibitors. After 30 min incubation on ice, cells are homogenized using Glass-Teflon homogenizer and homogenates will be spun at 14,000 g for 15 min. Cytosolic extracts are used for western blot analysis using anti-cytochrome C monoclonal antibody (PharMingen).

siRNA Transfection, Chemical Inhibitor, and Apoptosis Detection

Prostate cancer cell lines are transfected with gene specific and nonspecific control siRNAs (Dharmacon) using LipofectAMINE 2000 (Invitrogen). Optimum gene knock-down time and siRNA concentration are confirmed by western blot analysis and further evaluated for cell survival following drug treatment with or without CCL25, anti-CCL25 antibody, control antibody, and/or anti-CCR9 antibody. The detection of changes in live, apoptotic, and necrotic cells is evaluated as follows: cell survival is tested by Vybrant apoptosis as described by the manufacturer (Molecular probe), using FACScan flow cytometer and CellQuest™ software (BD Pharmingen). Change in down-stream gene expression after gene knockdown is tested using real-time PCR and western blotting.

Cells treated with CCL25 show enhanced expression of cell survival and drug transporter proteins which show differences in their expression pattern in hormone responsive and non responsive cells. Anti-CCL25 Abs effectively reverse the effect of CCL25 in PCa cells. Doxorubicin, estramustine, etoposide and docetaxel induce apoptosis in PCa cells without CCL25 treatment (or CCR9 blockade).

EXAMPLE 5

CCR9-CCL25 Induced Changes in ABC Drug Transporters

LNCaP, PC3, and DU145 cells are grown with or without CCL25, anti-CCL25 antibody, control antibody, and/or anti-CCR9 antibodies along with or without doxorubicin, estramustine, etoposide or docetaxel for 4, 8, 12 or 16 hours as described earlier. After treatment, changes in the ABC transporter and Twist-1 mRNA expression are quantified by real-time PCR, as described above, using specific primers directed for ABC and Twist-1 cDNA. The genes demonstrating significant alterations in mRNA expression are further tested by Western blot analysis. Nuclear extracts from treated cells are evaluated by chromatin immuno-precipitation (ChIP) assay to determine whether the transcriptional factors induced by CXCL16 bind the promoter region of ABC transporters and Twist-1.

Chromatin Immuno Precipitation (ChIP)

The results from Example 4 provide information about the genes that are regulated as well as those that may modulate transcription factors activated by CCR9-CCL25 interaction. Based on these results, target transcription factors and genes are selected. Specific PCR primers are designed against the promoter region of these genes containing the binding sites of transcription factors. PCR primer are used to amplify the DNA being precipitated along with transcription factors. Cells are harvested by trypsinization in the presence of 20 mM butyrate. 50,000 cells are re-suspended in 500 μl PBS/butyrate. Proteins and DNA are cross-linked with 1% formaldehyde for 8 min at room temperature and cross-linking is stopped with 125 mM glycine for 5 min. Cells are centrifuged at 470 g in a swing-out rotor with soft deceleration settings for 10 min at 4° C. and washed twice in 0.5 ml ice-cold PBS/butyrate by vortexing followed by centrifugation. Cells are lysed by addition of lysis buffer (50 mM Tris-HCl, pH 8, 10 mM EDTA, 1% SDS, protease inhibitor cocktail (Sigma-Aldrich), 1 mM PMSF, 20 mM butyrate, vortexing and subsequent centrifugation. This procedure is known to produce chromatin fragments of 500 bp. The sonicated lysate is diluted 8-fold in RIPA buffer containing a protease inhibitor cocktail, 1 mM PMSF, and 20 mM butyrate (RIPA ChIP buffer). RIPA ChIP buffer (330 μl) is added to the pellet and mixed by vortexing. Immunoprecipitation and washes of the ChIP material is accomplished by the use of antibody-directed against specific transcription factors. Chromatin is aliquoted into tubes containing antibody-bead complexes. Input sample is placed in a tube for phenol-chloroform isoamyl alcohol isolation. The immunoprecipitated material is washed three times and transferred into a new tube while in TE. DNA elution in 1% SDS, cross-link reversal and proteinase K digestion is carried out in a single step for 2 hrs at 68° C. DNA is extracted with phenol-chloroform isoamylalcohol, and ethanol-precipitation in presence of acrylamide carrier (Sigma-Aldrich) and dissolved in TE. Immunoprecipitated DNA from 3-4 independent ChIPs is analyzed by real time PCR. Real-time PCR data is expressed as percent (±SD) precipitated (antibody-bound) DNA relative to input DNA, in three independent replicate ChIP assays.

Phosphorylation and activation of transcription factors such as CREB, Fos, Jun, and NFkB via CXCR6-CXCL16 signaling subsequently leads to increases in expression of ABC transporters and Twist-1. Decreases in gene expression are observed if negative regulatory elements are present in the same promoter. Since hormone-dependent and refractory PCa cells have differences in the expression of these intracellular signaling molecules, they show variations in genes to be modulated by hormone dependent and refractory conditions. The modulation in gene expression shows differences with drug treatment in presence of CXCL16 and in absence of CXCL16 treatment.

EXAMPLE 6

In Vivo Evaluation of CCL25-Directed Therapy

Male nude mice are subcutaneously challenged by luciferase expressing androgen responsive (LNCaP-Luc) and non-responsive (PC3-Luc) cells. Tumor development is measured non-invasively using in vivo imaging system. After establishment of a measurable tumor, mice are divided into treatment (A, B, C, D and E) and control groups (F, G, H, I, J and K). Group "A" receives CCL25 neutralizing antibodies (12.5 mg/kg/day) every alternate day and controls (group F) receive isotype control antibodies (12.5 mg/kg/day). Group "B," "C," "D" and "E" receive CCL25 neutralizing antibodies (12.5 mg/kg/day) with intraperitoneal injection of doxorubicin (5 mg/kg/day on days 1 to 3 followed by administration on days 15 to 17), intravenous injection of etoposide (10 mg/kg/day; on day 1, 5, 9, 14, 19 and 24), intravenous injection of estramustine (4 mg/kg/day on day 1-5 and day 26-31), or intraperitoneal injection of docetaxel (8 mg/kg/day twice a week for 4 weeks), respectively. Controls for these treatment groups ("G," "H," "I" and "J," respectively) receive theses drugs using similar concentration and injection protocol with isotype control antibodies (12.5 mg/kg/day). Group "K" receives PBS and serves as placebo. Tumor progression and regression in treatment and controls are evaluated by non-invasive in vivo imaging. The tumor from treated groups and untreated control groups is excised and evaluated for the changes in the cell survival and drug resistance proteins by immunohistochemistry. In the context used herein, the term "CCL25 neutralizing antibodies" means anti-CCL25 antibodies and/or anti-CCR9 antibodies.

Statistics (Significance) and Sample Size

Sample size (or power) calculations are relevant to the design of preliminary studies and determining the requirements for proposed experiments. To interpret our results, significance tests and statistical analysis are also critical. The traditional α-value, i.e., p=0.01, is used to evaluate the statistical significance of this study. The proposed experiment will require a minimum of 10 mice per group. The data is expressed as the mean±SEM and compared using a two-tailed paired (or unpaired) student's t-test for normally distributed samples or an unpaired Mann Whitney U test as a non-parametric test for samples not normally distributed. The results are analyzed using SYSTAT (Systat software Inc.) statistical program. Single-factor and two-factor variance ANOVA analyses are used to evaluate groups and subgroups, respectively. Hence, results are considered statistically significant if p values are <0.05.

Animals:

Six to eight week old male nude mice are subcutaneously injected with PCa cells. Briefly, 5×10^6 Luciferase expressing PC3 cells are resuspended in 100 μl of sterile PBS and injected into the flanks of nude mice under isoflurane anesthesia. Luciferase expressing LNCaP cells (5×10^6 cell) are mixed with 50% Matrigel (Becton Dickinson) and injected in the flanks of nude mice under isoflurane anesthesia.

Analysis of In Vivo Tumor Growth

Tumor bearing nude mice receive 150 mg/kg D-Luciferin (Xenogen) by intraperitoneal injection Using 25×⅝" gauge needle 15 minutes before imaging. The mice are imaged using the IVIS100 in vivo imaging system and results expressed in photons/sec/cm^2/sr. Tumor volume is measured by use of calipers and calculated by the formula (Larger diameter)×(smaller diameter)^2×0.5.

Cell Survival, Apoptotic and Drug Resistant Gene Expression Analysis

Tumors from all groups are excised three days after completion of treatment protocols. Tumors are fixed in 4% PFA and embedded in paraffin. Paraffin sections (thickness 7 μm) are mounted on glass slides, deparaffinized and re-hydrated (Xylene for 5 min; absolute, 95% and 70% ethanol for 1 min each). The rehydrated sections are used for peroxidase based immunohistochemical staining for drug transporters, PI3K, Akt, FAK, FKHR, FOXO, Apaf1, Bax, Bcl2, $BclX_L$, BaK, Bad, Bid, XIAP, Bik, Bim, TP53, Cytochrome C, Caspase-3, -6, -8, -9, survivin, lamin, CamKII, vitronectin, β-Catenin, cadherins, Twist-1, CREB, NF-κB, Myc, Fos, Jun, CCR9 and CCL25. After staining, slides are scanned and analyzed by the Aperio scanscope (Aperio) system.

CCL25 neutralization leads to decreased cell survival in response to drugs, thus reduction of tumor volume. However, the response also varies among the tumors formed by hormone sensitive (LNCaP) and hormone refractory (PC3 cells). Further, chemotherapeutic drugs have lower efficacy in the tumors with a functional CCR9-CCL25 axis, which may enhance the expression of ABC proteins known to transport these drugs out of the cell.

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present application, and is not intended to detail all those obvious modifications and variations of it that will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present application, which is defined by the following claims. The claims are intended to cover the components and steps in any sequence that is effective to meet the objectives there intended, unless the context specifically indicates the contrary. All the references cited in the specification are herein incorporated by reference in their entirety.

SEQUENCE LISTING

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Phe Thr Gly Met Pro Pro Ala Asp Glu Asp Tyr Ser Pro Cys Met Leu
            20                  25                  30

Glu Thr Glu Thr Leu Asn Lys Tyr Val Val Ile Ile Ala Tyr Ala Leu
        35                  40                  45

Val Phe Leu Leu Ser Leu Leu Gly Asn Ser Leu Val Met Leu Val Ile
    50                  55                  60

Leu Tyr Ser Arg Val Gly Arg Ser Val Thr Asp Val Tyr Leu Leu Asn
65                  70                  75                  80

Leu Ala Leu Ala Asp Leu Leu Phe Ala Leu Thr Leu Pro Ile Trp Ala
                85                  90                  95

Ala Ser Lys Val Asn Gly Trp Ile Phe Gly Thr Phe Leu Cys Lys Val
            100                 105                 110

Val Ser Leu Leu Lys Glu Val Asn Phe Tyr Ser Gly Ile Leu Leu Leu
        115                 120                 125

Ala Cys Ile Ser Val Asp Arg Tyr Leu Ala Ile Val His Ala Thr Arg
    130                 135                 140

Thr Leu Thr Gln Lys Arg His Leu Val Lys Phe Val Cys Leu Gly Cys
145                 150                 155                 160

Trp Gly Leu Ser Met Asn Leu Ser Leu Pro Phe Phe Leu Phe Arg Gln
                165                 170                 175

Ala Tyr His Pro Asn Asn Ser Ser Pro Val Cys Tyr Glu Val Leu Gly
            180                 185                 190

Asn Asp Thr Ala Lys Trp Arg Met Val Leu Arg Ile Leu Pro His Thr
        195                 200                 205

Phe Gly Phe Ile Val Pro Leu Phe Val Met Leu Phe Cys Tyr Gly Phe
    210                 215                 220

Thr Leu Arg Thr Leu Phe Lys Ala His Met Gly Gln Lys His Arg Ala
225                 230                 235                 240

Met Arg Val Ile Phe Ala Val Val Leu Ile Phe Leu Leu Cys Trp Leu
                245                 250                 255

Pro Tyr Asn Leu Val Leu Leu Ala Asp Thr Leu Met Arg Thr Gln Val
            260                 265                 270

Ile Gln Glu Ser Cys Glu Arg Arg Asn Asn Ile Gly Arg Ala Leu Asp
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        275                 280                 285

Ala Thr Glu Ile Leu Gly Phe Leu His Ser Cys Leu Asn Pro Ile Ile
    290                 295                 300

Tyr Ala Phe Ile Gly Gln Asn Phe Arg His Gly Phe Leu Lys Ile Leu
305                 310                 315                 320

Ala Met His Gly Leu Val Ser Lys Glu Phe Leu Ala Arg His Arg Val
                325                 330                 335

Thr Ser Tyr Thr Ser Ser Ser Val Asn Val Ser Ser Asn Leu
            340                 345                 350


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            20                  25                  30

Leu Leu Asp Ala Ala Pro Cys Glu Pro Glu Ser Leu Glu Ile Asn Lys
        35                  40                  45

Tyr Phe Val Val Ile Ile Tyr Ala Leu Val Phe Leu Leu Ser Leu Leu
    50                  55                  60

Gly Asn Ser Leu Val Met Leu Val Ile Leu Tyr Ser Arg Val Gly Arg
65                  70                  75                  80

Ser Val Thr Asp Val Tyr Leu Leu Asn Leu Ala Leu Ala Asp Leu Leu
                85                  90                  95

Phe Ala Leu Thr Leu Pro Ile Trp Ala Ala Ser Lys Val Asn Gly Trp
            100                 105                 110

Ile Phe Gly Thr Phe Leu Cys Lys Val Val Ser Leu Leu Lys Glu Val
        115                 120                 125

Asn Phe Tyr Ser Gly Ile Leu Leu Leu Ala Cys Ile Ser Val Asp Arg
    130                 135                 140

Tyr Leu Ala Ile Val His Ala Thr Arg Thr Leu Thr Gln Lys Arg Tyr
145                 150                 155                 160

Leu Val Lys Phe Ile Cys Leu Ser Ile Trp Gly Leu Ser Leu Leu Leu
                165                 170                 175

Ala Leu Pro Val Leu Leu Phe Arg Arg Thr Val Tyr Ser Ser Asn Val
            180                 185                 190

Ser Pro Ala Cys Tyr Glu Asp Met Gly Asn Asn Thr Ala Asn Trp Arg
        195                 200                 205

Met Leu Leu Arg Ile Leu Pro Gln Ser Phe Gly Phe Ile Val Pro Leu
    210                 215                 220

Leu Ile Met Leu Phe Cys Tyr Gly Phe Thr Leu Arg Thr Leu Phe Lys
225                 230                 235                 240

Ala His Met Gly Gln Lys His Arg Ala Met Arg Val Ile Phe Ala Val
                245                 250                 255

Val Leu Ile Phe Leu Leu Cys Trp Leu Pro Tyr Asn Leu Val Leu Leu
            260                 265                 270

Ala Asp Thr Leu Met Arg Thr Gln Val Ile Gln Glu Thr Cys Glu Arg
        275                 280                 285

Arg Asn His Ile Asp Arg Ala Leu Asp Ala Thr Glu Ile Leu Gly Ile
    290                 295                 300
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Leu His Ser Cys Leu Asn Pro Leu Ile Tyr Ala Phe Ile Gly Gln Lys
305                 310                 315                 320

Phe Arg His Gly Leu Leu Lys Ile Leu Ala Ile His Gly Leu Ile Ser
                325                 330                 335

Lys Asp Ser Leu Pro Lys Asp Ser Arg Pro Ser Phe Val Gly Ser Ser
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Ser Gly His Thr Ser Thr Thr Leu
        355                 360


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Arg Val Ala Leu Leu Leu Leu Leu Leu Val Ala Ala Gly Arg Arg Ala
            20                  25                  30

Ala Gly Ala Ser Val Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr
        35                  40                  45

Leu Gln Gly Ile His Pro Lys Asn Ile Gln Ser Val Asn Val Lys Ser
    50                  55                  60

Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn
65                  70                  75                  80

Gly Arg Lys Ala Cys Leu Asn Pro Ala Ser Pro Ile Val Lys Lys Ile
                85                  90                  95

Ile Glu Lys Met Leu Asn Ser Asp Lys Ser Asn
            100                 105


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Arg Val Ala Leu Leu Leu Leu Leu Leu Val Ala Ala Ser Arg Arg Ala
            20                  25                  30

Ala Gly Ala Pro Leu Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr
        35                  40                  45

Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Lys Val Lys Ser
    50                  55                  60

Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn
65                  70                  75                  80

Gly Gln Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Lys Lys Ile
                85                  90                  95

Ile Glu Lys Met Leu Lys Asn Gly Lys Ser Asn
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<400> SEQUENCE: 5

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1               5                   10                  15

Arg Val Ala Leu Leu Leu Leu Leu Leu Val Ala Ala Ser Arg Arg Ala
            20                  25                  30

Ala Gly Ala Ser Val Val Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr
        35                  40                  45

Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Asn Val Arg Ser
    50                  55                  60

Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn
65                  70                  75                  80

Gly Lys Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Gln Lys Ile
                85                  90                  95

Ile Glu Lys Ile Leu Asn Lys Gly Ser Thr Asn
            100                 105


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Ser Leu Cys Ala Leu Leu Val Leu Leu Leu Leu Leu Thr Gln Pro Gly
            20                  25                  30

Pro Ile Ala Ser Ala Gly Pro Ala Ala Ala Val Leu Arg Glu Leu Arg
        35                  40                  45

Cys Val Cys Leu Gln Thr Thr Gln Gly Val His Pro Lys Met Ile Ser
    50                  55                  60

Asn Leu Gln Val Phe Ala Ile Gly Pro Gln Cys Ser Lys Val Glu Val
65                  70                  75                  80

Val Ala Ser Leu Lys Asn Gly Lys Glu Ile Cys Leu Asp Pro Glu Ala
                85                  90                  95

Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Gly Gly Asn Lys
            100                 105                 110

Glu Asn


<210> SEQ ID NO 7
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<212> TYPE: PRT
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Ser Leu Cys Ala Leu Leu Ala Leu Leu Leu Leu Leu Thr Pro Pro Gly
            20                  25                  30

Pro Leu Ala Ser Ala Gly Pro Val Ser Ala Val Leu Thr Glu Leu Arg
        35                  40                  45

Cys Thr Cys Leu Arg Val Thr Leu Arg Val Asn Pro Lys Thr Ile Gly
    50                  55                  60

Lys Leu Gln Val Phe Pro Ala Gly Pro Gln Cys Ser Lys Val Glu Val
65                  70                  75                  80

Val Ala Ser Leu Lys Asn Gly Lys Gln Val Cys Leu Asp Pro Glu Ala
                85                  90                  95

Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Ser Gly Asn Lys
            100                 105                 110
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Lys Asn

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Leu His Ala Leu Gln Val Leu Leu Leu Leu Ser Leu Leu Leu Thr Ala
            20                  25                  30

Leu Ala Ser Ser Thr Lys Gly Gln Thr Lys Arg Asn Leu Ala Lys Gly
        35                  40                  45

Lys Glu Glu Ser Leu Asp Ser Asp Leu Tyr Ala Glu Leu Arg Cys Met
    50                  55                  60

Cys Ile Lys Thr Thr Ser Gly Ile His Pro Lys Asn Ile Gln Ser Leu
65                  70                  75                  80

Glu Val Ile Gly Lys Gly Thr His Cys Asn Gln Val Glu Val Ile Ala
                85                  90                  95

Thr Leu Lys Asp Gly Arg Lys Ile Cys Leu Asp Pro Asp Ala Pro Arg
            100                 105                 110

Ile Lys Lys Ile Val Gln Lys Lys Leu Ala Gly Asp Glu Ser Ala Asp
        115                 120                 125
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            20                  25                  30

Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe
        35                  40                  45

Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
    50                  55                  60

Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
65                  70                  75                  80

Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
                85                  90                  95

Glu Asn Ser
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            20                  25                  30

Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
        35                  40                  45
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Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
    50                  55                  60

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
65                  70                  75                  80

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
                85                  90                  95

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
            100                 105                 110

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
        115                 120                 125

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
    130                 135                 140

Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val
145                 150                 155                 160

Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn
                165                 170                 175

Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn
            180                 185                 190

Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu
        195                 200                 205

Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser
    210                 215                 220

Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr
225                 230                 235                 240

Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr
                245                 250                 255

Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln
            260                 265                 270

Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu
        275                 280                 285

Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe
    290                 295                 300

Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val
305                 310                 315                 320

Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly
                325                 330                 335

His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser Phe His Ser Ser
            340                 345                 350
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Cys Leu Ser Asp Gly Lys Pro Val Ser Leu Ser Tyr Arg Cys Pro Cys
            20                  25                  30

Arg Phe Phe Glu Ser His Val Ala Arg Ala Asn Val Lys His Leu Lys
        35                  40                  45

Ile Leu Asn Thr Pro Asn Cys Ala Leu Gln Ile Val Ala Arg Leu Lys
    50                  55                  60

Asn Asn Asn Arg Gln Val Cys Ile Asp Pro Lys Leu Lys Trp Ile Gln
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65                  70                  75                  80

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<210> SEQ ID NO 12
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Phe Leu Leu Gly Val Ile Gly Asn Val Leu Val Leu Val Ile Leu Glu
            20                  25                  30

Arg His Arg Gln Thr Arg Ser Ser Thr Glu Thr Phe Leu Phe His Leu
        35                  40                  45

Ala Val Ala Asp Leu Leu Leu Val Phe Ile Leu Pro Phe Ala Val Ala
    50                  55                  60

Glu Gly Ser Val Gly Trp Val Leu Gly Thr Phe Leu Cys Lys Thr Val
65                  70                  75                  80

Ile Ala Leu His Lys Val Asn Phe Tyr Cys Ser Ser Leu Leu Leu Ala
                85                  90                  95

Cys Ile Ala Val Asp Arg Tyr Leu Ala Ile Val His Ala Val His Ala
            100                 105                 110

Tyr Arg His Arg Arg Leu Leu Ser Ile His Ile Thr Cys Gly Thr Ile
        115                 120                 125

Trp Leu Val Gly Phe Leu Leu Ala Leu Pro Glu Ile Leu Phe Ala Lys
    130                 135                 140

Val Ser Gln Gly His His Asn Asn Ser Leu Pro Arg Cys Thr Phe Ser
145                 150                 155                 160

Gln Glu Asn Gln Ala Glu Thr His Ala Trp Phe Thr Ser Arg Phe Leu
                165                 170                 175

Tyr His Val Ala Gly Phe Leu Leu Pro Met Leu Val Met Gly Trp Cys
            180                 185                 190

Tyr Val Gly Val Val His Arg Leu Arg Gln Ala Gln Arg Arg Pro Gln
        195                 200                 205

Arg Gln Lys Ala Val Arg Val Ala Ile Leu Val Thr Ser Ile Phe Phe
    210                 215                 220

Leu Cys Trp Ser Pro Tyr His Ile Val Ile Phe Leu Asp Thr Leu Ala
225                 230                 235                 240

Arg Leu Lys Ala Val Asp Asn Thr Cys Lys Leu Asn Gly Ser Leu Pro
                245                 250                 255

Val Ala Ile Thr Met Cys Glu Phe Leu Gly Leu Ala His Cys Cys Leu
            260                 265                 270

Asn Pro Met Leu Tyr Thr Phe Ala Gly Val Lys Phe Arg Ser Asp Leu
        275                 280                 285

Ser Arg Leu Leu Thr Lys Leu Gly Cys Thr Gly Pro Ala Ser Leu Cys
    290                 295                 300

Gln Leu Phe Pro Ser Trp Arg Arg Ser Ser Leu Ser Glu Ser Glu Asn
305                 310                 315                 320

Ala Thr Ser Leu Thr Thr Phe
                325


<210> SEQ ID NO 13
<211> LENGTH: 372
```

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

```
Met Asn Tyr Pro Leu Thr Leu Glu Met Asp Leu Glu Asn Leu Glu Asp
1               5                   10                  15

Leu Phe Trp Glu Leu Asp Arg Leu Asp Asn Tyr Asn Asp Thr Ser Leu
            20                  25                  30

Val Glu Asn His Leu Cys Pro Ala Thr Glu Gly Pro Leu Met Ala Ser
        35                  40                  45

Phe Lys Ala Val Phe Val Pro Val Ala Tyr Ser Leu Ile Phe Leu Leu
    50                  55                  60

Gly Val Ile Gly Asn Val Leu Val Leu Val Ile Leu Glu Arg His Arg
65                  70                  75                  80

Gln Thr Arg Ser Ser Thr Glu Thr Phe Leu Phe His Leu Ala Val Ala
                85                  90                  95

Asp Leu Leu Leu Val Phe Ile Leu Pro Phe Ala Val Ala Glu Gly Ser
            100                 105                 110

Val Gly Trp Val Leu Gly Thr Phe Leu Cys Lys Thr Val Ile Ala Leu
        115                 120                 125

His Lys Val Asn Phe Tyr Cys Ser Ser Leu Leu Leu Ala Cys Ile Ala
    130                 135                 140

Val Asp Arg Tyr Leu Ala Ile Val His Ala Val His Ala Tyr Arg His
145                 150                 155                 160

Arg Arg Leu Leu Ser Ile His Ile Thr Cys Gly Thr Ile Trp Leu Val
                165                 170                 175

Gly Phe Leu Leu Ala Leu Pro Glu Ile Leu Phe Ala Lys Val Ser Gln
            180                 185                 190

Gly His His Asn Asn Ser Leu Pro Arg Cys Thr Phe Ser Gln Glu Asn
        195                 200                 205

Gln Ala Glu Thr His Ala Trp Phe Thr Ser Arg Phe Leu Tyr His Val
    210                 215                 220

Ala Gly Phe Leu Leu Pro Met Leu Val Met Gly Trp Cys Tyr Val Gly
225                 230                 235                 240

Val Val His Arg Leu Arg Gln Ala Gln Arg Arg Pro Gln Arg Gln Lys
                245                 250                 255

Ala Val Arg Val Ala Ile Leu Val Thr Ser Ile Phe Phe Leu Cys Trp
            260                 265                 270

Ser Pro Tyr His Ile Val Ile Phe Leu Asp Thr Leu Ala Arg Leu Lys
        275                 280                 285

Ala Val Asp Asn Thr Cys Lys Leu Asn Gly Ser Leu Pro Val Ala Ile
    290                 295                 300

Thr Met Cys Glu Phe Leu Gly Leu Ala His Cys Cys Leu Asn Pro Met
305                 310                 315                 320

Leu Tyr Thr Phe Ala Gly Val Lys Phe Arg Ser Asp Leu Ser Arg Leu
                325                 330                 335

Leu Thr Lys Leu Gly Cys Thr Gly Pro Ala Ser Leu Cys Gln Leu Phe
            340                 345                 350

Pro Ser Trp Arg Arg Ser Ser Leu Ser Glu Ser Glu Asn Ala Thr Ser
        355                 360                 365

Leu Thr Thr Phe
    370
```

<210> SEQ ID NO 14

<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

```
Met Lys Phe Ile Ser Thr Ser Leu Leu Leu Met Leu Leu Val Ser Ser
1               5                   10                  15

Leu Ser Pro Val Gln Gly Val Leu Glu Val Tyr Tyr Thr Ser Leu Arg
            20                  25                  30

Cys Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile
        35                  40                  45

Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu
    50                  55                  60

Ile Ile Val Trp Lys Lys Asn Lys Ser Ile Val Cys Val Asp Pro Gln
65                  70                  75                  80

Ala Glu Trp Ile Gln Arg Met Met Glu Val Leu Arg Lys Arg Ser Ser
                85                  90                  95

Ser Thr Leu Pro Val Pro Val Phe Lys Arg Lys Ile Pro
            100                 105
```

<210> SEQ ID NO 15
<211> LENGTH: 342
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

```
Met Ala Glu His Asp Tyr His Glu Asp Tyr Gly Phe Ser Ser Phe Asn
1               5                   10                  15

Asp Ser Ser Gln Glu Glu His Gln Asp Phe Leu Gln Phe Ser Lys Val
            20                  25                  30

Phe Leu Pro Cys Met Tyr Leu Val Val Phe Val Cys Gly Leu Val Gly
        35                  40                  45

Asn Ser Leu Val Leu Val Ile Ser Ile Phe Tyr His Lys Leu Gln Ser
    50                  55                  60

Leu Thr Asp Val Phe Leu Val Asn Leu Pro Leu Ala Asp Leu Val Phe
65                  70                  75                  80

Val Cys Thr Leu Pro Phe Trp Ala Tyr Ala Gly Ile His Glu Trp Val
                85                  90                  95

Phe Gly Gln Val Met Cys Lys Ser Leu Leu Gly Ile Tyr Thr Ile Asn
            100                 105                 110

Phe Tyr Thr Ser Met Leu Ile Leu Thr Cys Ile Thr Val Asp Arg Phe
        115                 120                 125

Ile Val Val Val Lys Ala Thr Lys Ala Tyr Asn Gln Gln Ala Lys Arg
    130                 135                 140

Met Thr Trp Gly Lys Val Thr Ser Leu Leu Ile Trp Val Ile Ser Leu
145                 150                 155                 160

Leu Val Ser Leu Pro Gln Ile Ile Tyr Gly Asn Val Phe Asn Leu Asp
                165                 170                 175

Lys Leu Ile Cys Gly Tyr His Asp Glu Ala Ile Ser Thr Val Val Leu
            180                 185                 190

Ala Thr Gln Met Thr Leu Gly Phe Phe Leu Pro Leu Leu Thr Met Ile
        195                 200                 205

Val Cys Tyr Ser Val Ile Ile Lys Thr Leu Leu His Ala Gly Gly Phe
    210                 215                 220

Gln Lys His Arg Ser Leu Lys Ile Ile Phe Leu Val Met Ala Val Phe
225                 230                 235                 240
```

```
Leu Leu Thr Gln Met Pro Phe Asn Leu Met Lys Phe Ile Arg Ser Thr
                245                 250                 255

His Trp Glu Tyr Tyr Ala Met Thr Ser Phe His Tyr Thr Ile Met Val
            260                 265                 270

Thr Glu Ala Ile Ala Tyr Leu Arg Ala Cys Leu Asn Pro Val Leu Tyr
        275                 280                 285

Ala Phe Val Ser Leu Lys Phe Arg Lys Asn Phe Trp Lys Leu Val Lys
    290                 295                 300

Asp Ile Gly Cys Leu Pro Tyr Leu Gly Val Ser His Gln Trp Lys Ser
305                 310                 315                 320

Ser Glu Asp Asn Ser Lys Thr Phe Ser Ala Ser His Asn Val Glu Ala
                325                 330                 335

Thr Ser Met Phe Gln Leu
            340


<210> SEQ ID NO 16
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Lys Val Ser Glu Ala Ala Leu Ser Leu Leu Val Leu Ile Leu Ile
1               5                   10                  15

Ile Thr Ser Ala Ser Arg Ser Gln Pro Lys Val Pro Glu Trp Val Asn
            20                  25                  30

Thr Pro Ser Thr Cys Cys Leu Lys Tyr Tyr Glu Lys Val Leu Pro Arg
        35                  40                  45

Arg Leu Val Val Gly Tyr Arg Lys Ala Leu Asn Cys His Leu Pro Ala
    50                  55                  60

Ile Ile Phe Val Thr Lys Arg Asn Arg Glu Val Cys Thr Asn Pro Asn
65                  70                  75                  80

Asp Asp Trp Val Gln Glu Tyr Ile Lys Asp Pro Asn Leu Pro Leu Leu
                85                  90                  95

Pro Thr Arg Asn Leu Ser Thr Val Lys Ile Ile Thr Ala Lys Asn Gly
            100                 105                 110

Gln Pro Gln Leu Leu Asn Ser Gln
        115                 120


<210> SEQ ID NO 17
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Lys Val Ser Glu Ala Ala Leu Ser Leu Leu Val Leu Ile Leu Ile
1               5                   10                  15

Ile Thr Ser Ala Ser Arg Ser Gln Pro Lys Val Pro Glu Trp Val Asn
            20                  25                  30

Thr Pro Ser Thr Cys Cys Leu Lys Tyr Tyr Glu Lys Val Leu Pro Arg
        35                  40                  45

Arg Leu Val Val Gly Tyr Arg Lys Ala Leu Asn Cys His Leu Pro Ala
    50                  55                  60

Ile Ile Phe Val Thr Lys Arg Asn Arg Glu Val Cys Thr Asn Pro Asn
65                  70                  75                  80

Asp Asp Trp Val Gln Glu Tyr Ile Lys Asp Pro Asn Leu Pro Leu Leu
                85                  90                  95
```

```
Pro Thr Arg Asn Leu Ser Thr Val Lys Ile Ile Thr Ala Lys Asn Gly
            100                 105                 110

Gln Pro Gln Leu Leu Asn Ser Gln
        115                 120


<210> SEQ ID NO 18
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Asn Leu Trp Leu Leu Ala Cys Leu Val Ala Gly Phe Leu Gly Ala
1               5                   10                  15

Trp Ala Pro Ala Val His Thr Gln Gly Val Phe Glu Asp Cys Cys Leu
            20                  25                  30

Ala Tyr His Tyr Pro Ile Gly Trp Ala Val Leu Arg Arg Ala Trp Thr
        35                  40                  45

Tyr Arg Ile Gln Glu Val Ser Gly Ser Cys Asn Leu Pro Ala Ala Ile
    50                  55                  60

Phe Tyr Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys Ser
65                  70                  75                  80

Arg Glu Val Gln Arg Ala Met Lys Leu Leu Asp Ala Arg Asn Lys Val
                85                  90                  95

Phe Ala Lys Leu His His Asn Thr Gln Thr Phe Gln Ala Gly Pro His
            100                 105                 110

Ala Val Lys Lys Leu Ser Ser Gly Asn Ser Lys Leu Ser Ser Ser Lys
        115                 120                 125

Phe Ser Asn Pro Ile Ser Ser Ser Lys Arg Asn Val Ser Leu Leu Ile
    130                 135                 140

Ser Ala Asn Ser Gly Leu
145                 150


<210> SEQ ID NO 19
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Asn Leu Trp Leu Leu Ala Cys Leu Val Ala Gly Phe Leu Gly Ala
1               5                   10                  15

Trp Ala Pro Ala Val His Thr Gln Gly Val Phe Glu Asp Cys Cys Leu
            20                  25                  30

Ala Tyr His Tyr Pro Ile Gly Trp Ala Val Leu Arg Arg Ala Trp Thr
        35                  40                  45

Tyr Arg Ile Gln Glu Val Ser Gly Ser Cys Asn Leu Pro Ala Ala Ile
    50                  55                  60

Phe Tyr Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys Ser
65                  70                  75                  80

Arg Glu Val Gln Arg Ala Met Lys Leu Leu Asp Ala Arg Asn Lys Val
                85                  90                  95

Phe Ala Lys Leu His His Asn Thr Gln Thr Phe Gln Ala Gly Pro His
            100                 105                 110

Ala Val Lys Lys Leu Ser Ser Gly Asn Ser Lys Leu Ser Ser Ser Lys
        115                 120                 125

Phe Ser Asn Pro Ile Ser Ser Ser Lys Arg Asn Val Ser Leu Leu Ile
    130                 135                 140
```

Ser Ala Asn Ser Gly Leu
145 150

<210> SEQ ID NO 20
<211> LENGTH: 84
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Asn Leu Trp Leu Leu Ala Cys Leu Val Ala Gly Phe Leu Gly Ala
1 5 10 15

Trp Ala Pro Ala Val His Thr Gln Gly Val Phe Glu Asp Cys Cys Leu
20 25 30

Ala Tyr His Tyr Pro Ile Gly Trp Ala Val Leu Arg Arg Ala Trp Thr
35 40 45

Tyr Arg Ile Gln Glu Val Ser Gly Ser Cys Asn Leu Pro Ala Ala Ile
50 55 60

Arg Pro Ser Cys Cys Lys Glu Val Glu Phe Trp Lys Leu Gln Val Ile
65 70 75 80

Ile Val Gln Val

<210> SEQ ID NO 21
<211> LENGTH: 355
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Asp Gln Phe Pro Glu Ser Val Thr Glu Asn Phe Glu Tyr Asp Asp
1 5 10 15

Leu Ala Glu Ala Cys Tyr Ile Gly Asp Ile Val Val Phe Gly Thr Val
20 25 30

Phe Leu Ser Ile Phe Tyr Ser Val Ile Phe Ala Ile Gly Leu Val Gly
35 40 45

Asn Leu Leu Val Val Phe Ala Leu Thr Asn Ser Lys Lys Pro Lys Ser
50 55 60

Val Thr Asp Ile Tyr Leu Leu Asn Leu Ala Leu Ser Asp Leu Leu Phe
65 70 75 80

Val Ala Thr Leu Pro Phe Trp Thr His Tyr Leu Ile Asn Glu Lys Gly
85 90 95

Leu His Asn Ala Met Cys Lys Phe Thr Thr Ala Phe Phe Phe Ile Gly
100 105 110

Phe Phe Gly Ser Ile Phe Phe Ile Thr Val Ile Ser Ile Asp Arg Tyr
115 120 125

Leu Ala Ile Val Leu Ala Ala Asn Ser Met Asn Asn Arg Thr Val Gln
130 135 140

His Gly Val Thr Ile Ser Leu Gly Val Trp Ala Ala Ala Ile Leu Val
145 150 155 160

Ala Ala Pro Gln Phe Met Phe Thr Lys Gln Lys Glu Asn Glu Cys Leu
165 170 175

Gly Asp Tyr Pro Glu Val Leu Gln Glu Ile Trp Pro Val Leu Arg Asn
180 185 190

Val Glu Thr Asn Phe Leu Gly Phe Leu Leu Pro Leu Leu Ile Met Ser
195 200 205

Tyr Cys Tyr Phe Arg Ile Ile Gln Thr Leu Phe Ser Cys Lys Asn His
210 215 220

```
Lys Lys Ala Lys Ala Ile Lys Leu Ile Leu Leu Val Val Ile Val Phe
225                 230                 235                 240

Phe Leu Phe Trp Thr Pro Tyr Asn Val Met Ile Phe Leu Glu Thr Leu
                245                 250                 255

Lys Leu Tyr Asp Phe Phe Pro Ser Cys Asp Met Arg Lys Asp Leu Arg
            260                 265                 270

Leu Ala Leu Ser Val Thr Glu Thr Val Ala Phe Ser His Cys Cys Leu
        275                 280                 285

Asn Pro Leu Ile Tyr Ala Phe Ala Gly Glu Lys Phe Arg Arg Tyr Leu
    290                 295                 300

Tyr His Leu Tyr Gly Lys Cys Leu Ala Val Leu Cys Gly Arg Ser Val
305                 310                 315                 320

His Val Asp Phe Ser Ser Ser Glu Ser Gln Arg Ser Arg His Gly Ser
                325                 330                 335

Val Leu Ser Ser Asn Phe Thr Tyr His Thr Ser Asp Gly Asp Ala Leu
            340                 345                 350

Leu Leu Leu
        355


<210> SEQ ID NO 22
<211> LENGTH: 397
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Ala Pro Ile Ser Leu Ser Trp Leu Leu Arg Leu Ala Thr Phe Cys
1               5                   10                  15

His Leu Thr Val Leu Leu Ala Gly Gln His His Gly Val Thr Lys Cys
            20                  25                  30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
        35                  40                  45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
    50                  55                  60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65                  70                  75                  80

Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
                85                  90                  95

Thr Arg Asn Gly Gly Thr Phe Glu Lys Gln Ile Gly Glu Val Lys Pro
            100                 105                 110

Arg Thr Thr Pro Ala Ala Gly Gly Met Asp Glu Ser Val Val Leu Glu
        115                 120                 125

Pro Glu Ala Thr Gly Glu Ser Ser Ser Leu Glu Pro Thr Pro Ser Ser
    130                 135                 140

Gln Glu Ala Gln Arg Ala Leu Gly Thr Ser Pro Glu Leu Pro Thr Gly
145                 150                 155                 160

Val Thr Gly Ser Ser Gly Thr Arg Leu Pro Pro Thr Pro Lys Ala Gln
                165                 170                 175

Asp Gly Gly Pro Val Gly Thr Glu Leu Phe Arg Val Pro Pro Val Ser
            180                 185                 190

Thr Ala Ala Thr Trp Gln Ser Ser Ala Pro His Gln Pro Gly Pro Ser
        195                 200                 205

Leu Trp Ala Glu Ala Lys Thr Ser Glu Ala Pro Ser Thr Gln Asp Pro
    210                 215                 220

Ser Thr Gln Ala Ser Thr Ala Ser Ser Pro Ala Pro Glu Glu Asn Ala
225                 230                 235                 240
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```
Pro Ser Glu Gly Gln Arg Val Trp Gly Gln Gly Gln Ser Pro Arg Pro
                245                 250                 255

Glu Asn Ser Leu Glu Arg Glu Glu Met Gly Pro Val Pro Ala His Thr
            260                 265                 270

Asp Ala Phe Gln Asp Trp Gly Pro Gly Ser Met Ala His Val Ser Val
        275                 280                 285

Val Pro Val Ser Ser Glu Gly Thr Pro Ser Arg Glu Pro Val Ala Ser
    290                 295                 300

Gly Ser Trp Thr Pro Lys Ala Glu Glu Pro Ile His Ala Thr Met Asp
305                 310                 315                 320

Pro Gln Arg Leu Gly Val Leu Ile Thr Pro Val Pro Asp Ala Gln Ala
                325                 330                 335

Ala Thr Arg Arg Gln Ala Val Gly Leu Leu Ala Phe Leu Gly Leu Leu
            340                 345                 350

Phe Cys Leu Gly Val Ala Met Phe Thr Tyr Gln Ser Leu Gln Gly Cys
        355                 360                 365

Pro Arg Lys Met Ala Gly Glu Met Ala Glu Gly Leu Arg Tyr Ile Pro
    370                 375                 380

Arg Ser Cys Gly Ser Asn Ser Tyr Val Leu Val Pro Val
385                 390                 395


&lt;210&gt; SEQ ID NO 23
&lt;211&gt; LENGTH: 2502
&lt;212&gt; TYPE: DNA
&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 23

tattcatcaa gtgccctcta gctgttaagt cactctgatc tctgactgca gctcctactg      60

ttggacacac ctggccggtg cttcagttag atcaaaccat tgctgaaact gaagaggaca     120

tgtcaaatat tacagatcca cagatgtggg attttgatga tctaaatttc actggcatgc     180

cacctgcaga tgaagattac agcccctgta tgctagaaac tgagacactc aacaagtatg     240

ttgtgatcat cgcctatgcc ctagtgttcc tgctgagcct gctgggaaac tccctggtga     300

tgctggtcat cttatacagc agggtcggcc gctccgtcac tgatgtctac ctgctgaacc     360

tggccttggc cgacctactc tttgccctga ccttgcccat ctgggccgcc tccaaggtga     420

atggctggat ttttggcaca ttcctgtgca aggtggtctc actcctgaag gaagtcaact     480

tctacagtgg catcctgctg ttggcctgca tcagtgtgga ccgttacctg gccattgtcc     540

atgccacacg cacactgacc cagaagcgtc acttggtcaa gtttgtttgt cttggctgct     600

ggggactgtc tatgaatctg tccctgccct tcttcctttt ccgccaggct taccatccaa     660

acaattccag tccagtttgc tatgaggtcc tgggaaatga cacagcaaaa tggcggatgg     720

tgttgcggat cctgcctcac acctttggct tcatcgtgcc gctgtttgtc atgctgttct     780

gctatggatt caccctgcgt acactgttta aggcccacat ggggcagaag caccgagcca     840

tgagggtcat ctttgctgtc gtcctcatct tcctgctttg ctggctgccc tacaacctgg     900

tcctgctggc agacaccctc atgaggaccc aggtgatcca ggagagctgt gagcgccgca     960

acaacatcgg ccgggccctg gatgccactg agattctggg atttctccat agctgcctca    1020

accccatcat ctacgccttc atcggccaaa attttcgcca tggattcctc aagatcctgg    1080

ctatgcatgg cctggtcagc aaggagttct tggcacgtca tcgtgttacc tcctacactt    1140

cttcgtctgt caatgtctct tccaacctct gaaaaccatc gatgaaggaa tatctcttct    1200
```

```
cagaaggaaa gaataaccaa caccctgagg ttgtgtgtgg aaggtgatct ggctctggac   1260

aggcactatc tgggttttgg ggggacgcta taggatgtgg ggaagttagg aactggtgtc   1320

ttcaggggcc acaccaacct tctgaggagc tgttgaggta cctccaagga ccggcctttg   1380

cacctccatg gaaacgaagc accatcattc ccgttgaacg tcacatcttt aacccactaa   1440

ctggctaatt agcatggcca catctgagcc ccgaatctga cattagatga gagaacaggg   1500

ctgaagctgt gtcctcatga gggctggatg ctctcgttga ccctcacagg agcatctcct   1560

caactctgag tgttaagcgt tgagccacca agctggtggc tctgtgtgct ctgatccgag   1620

ctcagggggg tggttttccc atctcaggtg tgttgcagtg tctgctggag acattgaggc   1680

aggcactgcc aaaacatcaa cctgccagct ggccttgtga ggagctggaa acacatgttc   1740

cccttggggg tggtggatga acaaagagaa agagggtttg gaagccagat ctatgccaca   1800

agaacccccct ttacccccat gaccaacatc gcagacacat gtgctggcca cctgctgagc   1860

cccaagtgga acgagacaag cagcccttag cccttcccct ctgcagcttc caggctggcg   1920

tgcagcatca gcatccctag aaagccatgt gcagccacca gtccattggg caggcagatg   1980

ttcctaataa agcttctgtt ccgtgcttgt ccctgtggaa gtatcttggt tgtgacagag   2040

tcaagggtgt gtgcagcatt gttggctgtt cctgcagtag aatgggggca gcacctccta   2100

agaaggcacc tctctgggtt gaagggcagt gttccctggg gctttaactc ctgctagaac   2160

agtctcttga ggcacagaaa ctcctgttca tgcccatacc cctggccaag gaagatccct   2220

ttgtccacaa gtaaaaggaa atgctcctcc agggagtctc agcttcaccc tgaggtgagc   2280

atcatcttct gggttaggcc ttgcctaggc atagccctgc ctcaagctat gtgagctcac   2340

cagtccctcc ccaaatgctt tccatgagtt gcagtttttt cctagtctgt tttccctcct   2400

tggagacagg gccctgtcgg tttattcact gtatgtcctt ggtgcctgga gcctactaaa   2460

tgctcaataa ataatgatca caggaaaaaa aaaaaaaaaa aa                       2502
```

<210> SEQ ID NO 24
<211> LENGTH: 2880
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

```
aggttcaaaa cattcagaga cagaaggtgg atagacaaat ctccaccttc agactggtag     60

gctcctccag aagccatcag acaggaagat gtgaaaatcc ccagcactca tcccagaatc    120

actaagtggc acctgtcctg ggccaaagtc ccaggacaga cctcattgtt cctctgtggg    180

aatacctccc caggagggca tcctggattt ccccccttgca acccaggtca gaagtttcat    240

cgtcaaggtt gtttcatctt ttttttcctg tctaacagct ctgactacca cccaaccttg    300

aggcacagtg aagacatcgg tggccactcc aataacagca ggtcacagct gctcttctgg    360

aggtgtccta caggtgaaaa gcccagcgac ccagtcagga tttaagttta cctcaaaaat    420

ggaagatttt aacatggaga gtgacagctt tgaagatttc tggaaaggtg aagatcttag    480

taattacagt tacagctcta ccctgccccc ttttctacta gatgccgccc catgtgaacc    540

agaatccctg gaaatcaaca agtattttgt ggtcattatc tatgccctgg tattcctgct    600

gagcctgctg ggaaactccc tcgtgatgct ggtcatctta tacagcaggg tcggccgctc    660

cgtcactgat gtctacctgc tgaacctagc cttggccgac ctactctttg ccctgacctt    720

gcccatctgg gccgcctcca aggtgaatgg ctggattttt ggcacattcc tgtgcaaggt    780

ggtctcactc ctgaaggaag tcaacttcta tagtggcatc ctgctactgg cctgcatcag    840
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```
tgtggaccgt tacctggcca ttgtccatgc cacacgcaca ctgacccaga agcgctactt     900

ggtcaaattc atatgtctca gcatctgggg tctgtccttg ctcctggccc tgcctgtctt     960

acttttccga aggaccgtct actcatccaa tgttagccca gcctgctatg aggacatggg    1020

caacaataca gcaaactggc ggatgctgtt acggatcctg ccccagtcct ttggcttcat    1080

cgtgccactg ctgatcatgc tgttctgcta cggattcacc ctgcgtacgc tgtttaaggc    1140

ccacatgggg cagaagcacc gggccatgcg ggtcatcttt gctgtcgtcc tcatcttcct    1200

gctctgctgg ctgccctaca acctggtcct gctggcagac accctcatga ggacccaggt    1260

gatccaggag acctgtgagc gccgcaatca catcgaccgg gctctggatg ccaccgagat    1320

tctgggcatc cttcacagct gcctcaaccc cctcatctac gccttcattg gccagaagtt    1380

tcgccatgga ctcctcaaga ttctagctat acatggcttg atcagcaagg actccctgcc    1440

caaagacagc aggccttcct ttgttggctc ttcttcaggg cacacttcca ctactctcta    1500

agacctcctg cctaagtgca gccccgtggg gttcctccct tctcttcaca gtcacattcc    1560

aagcctcatg tccactggtt cttcttggtc tcagtgtcaa tgcagccccc attgtggtca    1620

caggaagtag aggaggccac gttcttacta gtttcccttg catggtttag aaagcttgcc    1680

ctggtgcctc accccttgcc ataattacta tgtcatttgc tggagctctg cccatcctgc    1740

ccctgagccc atggcactct atgttctaag aagtgaaaat ctacactcca gtgagacagc    1800

tctgcatact cattaggatg gctagtatca aaagaaagaa aatcaggctg gccaacgggg    1860

tgaaaccctg tctctactaa aaatacaaaa aaaaaaaaaa attagccggg cgtggtggtg    1920

agtgcctgta atcacagcta cttgggaggc tgagatggga gaatcacttg aacccgggag    1980

gcagaggttg cagtgagccg agattgtgcc cctgcactcc agcctgagcg acagtgagac    2040

tctgtctcag tccatgaaga tgtagaggag aaactggaac tctcgagcgt tgctgggggg    2100

gattgtaaaa tggtgtgacc actgcagaag acagtatggc agctttcctc aaaacttcag    2160

acatagaatt aacacatgat cctgcaattc cacttatagg aattgaccca caagaaatga    2220

aagcagggac ttgaacccat atttgtacac caatattcat agcagcttat tcacaagacc    2280

caaaaggcag aagcaaccca aatgttcatc aatgaatgaa tgaatggcta agcaaaatgt    2340

gatatgtacc taacgaagta tccttcagcc tgaaagagga atgaagtact catacatgtt    2400

acaacacgga cgaaccttga aaactttatg ctaagtgaaa taagccagac atcaacagat    2460

aaatagttta tgattccacc tacatgaggt actgagagtg aacaaattta cagagacaga    2520

aagcagaaca gtgattacca gggactgagg ggaggggagc atgggaagtg acggtttaat    2580

gggcacaggg tttatgttta ggatgttgaa aaagttctgc agataaacag tagtgatagt    2640

tgtaccgcaa tgtgacttaa tgccactaaa ttgacactta aaaatggttt aaatggtcaa    2700

ttttgttatg tatattttat atcaatttaa aaaaaaacct gagccccaaa aggtatttta    2760

atcaccaagg ctgattaaac caaggctaga accacctgcc tatatttttt gttaaatgat    2820

ttcattcaat atcttttttt taataaacca tttttacttg ggtgtttata aaaaaaaaaa    2880
```

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<210> SEQ ID NO 25
<211> LENGTH: 1119
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca      60
```

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gacccgcctg ctgagcccca tggcccgcgc tgctctctcc gccgccccca gcaatccccg    120

gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg    180

agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc    240

caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt    300

catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa    360

gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa    420

gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag    480

agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga    540

agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg    600

taaaataatt aagggtatga ttaactctac ctgcacactg tcctattata ttcattcttt    660

ttgaaatgtc aaccccaagt tagttcaatc tggattcata tttaatttga aggtagaatg    720

ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc    780

actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg    840

gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga    900

aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt    960

ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt   1020

agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga   1080

atataaaaat aaagcactta tagaaaaaaa aaaaaaaaa                          1119
```

```
<210> SEQ ID NO 26
<211> LENGTH: 1234
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

gagctccggg aatttccctg gcccgggact ccgggctttc cagccccaac catgcataaa     60

aggggttcgc cgttctcgga gagccacaga gcccgggcca caggcagctc cttgccagct    120

ctcctcctcg cacagccgct cgaaccgcct gctgagcccc atggcccgcg ccacgctctc    180

cgccgccccc agcaatcccc ggctcctgcg ggtggcgctg ctgctcctgc tcctggtggc    240

cgccagccgg cgcgcagcag gagcgcccct ggccactgaa ctgcgctgcc agtgcttgca    300

gaccctgcag ggaattcacc tcaagaacat ccaaagtgtg aaggtgaagt cccccggacc    360

ccactgcgcc caaaccgaag tcatagccac actcaagaat gggcagaaag cttgtctcaa    420

ccccgcatcg cccatggtta agaaaatcat cgaaaagatg ctgaaaaatg gcaaatccaa    480

ctgaccagaa ggaaggagga agcttattgg tggctgttcc tgaaggaggc cctgccctta    540

caggaacaga agaggaaaga gagacacagc tgcagaggcc acctggattg cgcctaatgt    600

gtttgagcat cacttaggag aagtcttcta tttatttatt tatttattta tttgtttgtt    660

ttagaagatt ctatgttaat attttatgtg taaaataagg ttatgattga atctacttgc    720

acactctccc attatattta ttgtttattt taggtcaaac ccaagttagt tcaatcctga    780

ttcatattta atttgaagat agaaggtttg cagatattct ctagtcattt gttaatattt    840

cttcgtgatg acatatcaca tgtcagccac tgtgatagag gctgaggaat ccaagaaaat    900

ggccagtgag atcaatgtga cggcagggaa atgtatgtgt gtctattttg taactgtaaa    960

gatgaatgtc agttgttatt tattgaaatg atttcacagt gtgtggtcaa catttctcat   1020

gttgaagctt taagaactaa aatgttctaa atatcccttg gacattttat gtctttcttg   1080
```

taaggcatac tgccttgttt aatgttaatt atgcagtgtt tccctctgtg ttagagcaga 1140

gaggtttcga tatttattga tgttttcaca aagaacagga aaataaaata tttaaaaata 1200

taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1234

<210> SEQ ID NO 27
<211> LENGTH: 1166
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

gctccgggaa tttccctggc ccggccgctc cgggctttcc agtctcaacc atgcataaaa 60

agggttcgcc gatcttgggg agccacacag cccgggtcgc aggcacctcc ccgccagctc 120

tcccgcttct cgcacagctt cccgacgcgt ctgctgagcc ccatggccca cgccacgctc 180

tccgccgccc ccagcaatcc ccggctcctg cgggtggcgc tgctgctcct gctcctggtg 240

gccgccagcc ggcgcgcagc aggagcgtcc gtggtcactg aactgcgctg ccagtgcttg 300

cagacactgc agggaattca cctcaagaac atccaaagtg tgaatgtaag gtcccccgga 360

ccccactgcg cccaaaccga agtcatagcc acactcaaga atgggaagaa agcttgtctc 420

aaccccgcat cccccatggt tcagaaaatc atcgaaaaga tactgaacaa ggggagcacc 480

aactgacagg agagaagtaa gaagcttatc agcgtatcat tgacacttcc tgcagggtgg 540

tccctgccct taccagagct gaaaatgaaa aagagaacag cagctttcta gggacagctg 600

gaaaggactt aatgtgtttg actatttctt acgagggttc tacttattta tgtatttatt 660

tttgaaagct tgtattttaa tattttacat gctgttattt aaagatgtga gtgtgtttca 720

tcaaacatag ctcagtcctg attatttaat tggaatatga tgggttttaa atgtgtcatt 780

aaactaatat ttagtgggag accataatgt gtcagccacc ttgataaatg acagggtggg 840

gaactggagg gtggggggat tgaaatgcaa gcaattagtg gatcactgtt agggtaaggg 900

aatgtatgta cacatctatt ttttatactt tttttttaaa aaaagaatgt cagttgttat 960

ttattcaaat tatctcacat tatgtgttca acatttttat gctgaagttt cccttagaca 1020

ttttatgtct tgcttgtagg gcataatgcc ttgtttaatg tccattctgc agcgtttctc 1080

tttcccttgg aaaagagaat ttatcattac tgttacattt gtacaaatga catgataata 1140

aaagttttat gaaaaaaaaa aaaaaa 1166

<210> SEQ ID NO 28
<211> LENGTH: 2475
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

gtgcagaagg cacgaggaag ccacagtgct ccggatcctc caatcttcgc tcctccaatc 60

tccgctcctc cacccagttc aggaacccgc gaccgctcgc agcgctctct tgaccactat 120

gagcctcctg tccagccgcg cggcccgtgt ccccggtcct tcgagctcct tgtgcgcgct 180

gttggtgctg ctgctgctgc tgacgcagcc agggcccatc gccagcgctg gtcctgccgc 240

tgctgtgttg agagagctgc gttgcgtttg tttacagacc acgcaaggag ttcatcccaa 300

aatgatcagt aatctgcaag tgttcgccat aggcccacag tgctccaagg tggaagtggt 360

agcctccctg aagaacggga aggaaatttg tcttgatcca gaagcccctt ttctaaagaa 420

agtcatccag aaaattttgg acggtggaaa caaggaaaac tgattaagag aaatgagcac 480 gcatggaaaa gtttcccagt cttcagcaga gaagttttct ggaggtctct gaacccaggg 540

aagacaagaa ggaaagattt tgttgttgtt tgtttatttg tttttccagt agttagcttt 600

cttcctggat tcctcacttt gaagagtgtg aggaaaacct atgtttgccg cttaagcttt 660

cagctcagct aatgaagtgt ttagcatagt acctctgcta tttgctgtta ttttatctgc 720

tatgctattg aagttttggc aattgactat agtgtgagcc aggaatcact ggctgttaat 780

ctttcaaagt gtcttgaatt gtaggtgact attatatttc caagaaatat tccttaagat 840

attaactgag aaggctgtgg atttaatgtg gaaatgatgt ttcataagaa ttctgttgat 900

ggaaatacac tgttatcttc acttttataa gaaataggaa atattttaat gtttcttggg 960

gaatatgtta gagaatttcc ttactcttga ttgtgggata ctatttaatt atttcacttt 1020

agaaagctga gtgtttcaca ccttatctat gtagaatata tttccttatt cagaatttct 1080

aaaagtttaa gttctatgag ggctaatatc ttatcttcct ataattttag acattcttta 1140

tctttttagt atggcaaact gccatcattt acttttaaac tttgatttta tatgctattt 1200

attaagtatt ttattaggag taccataatt ctggtagcta aatatatatt ttagatagat 1260

gaagaagcta gaaaacaggc aaattcctga ctgctagttt atatagaaat gtattctttt 1320

agtttttaaa gtaaaggcaa acttaacaat gacttgtact ctgaaagttt tggaaacgta 1380

ttcaaacaat ttgaatataa atttatcatt tagttataaa aatatatagc gacatcctcg 1440

aggccctagc atttctcctt ggataggggа ccagagagag cttggaatgt taaaaacaaa 1500

acaaaacaaa aaaaaacaag gagaagttgt ccaagggatg tcaatttttt atccctctgt 1560

atgggttaga ttttccaaaa tcataatttg aagaaggcca gcatttatgg tagaatatat 1620

aattatatat aaggtggcca cgctggggca agttccctcc ccactcacag ctttggcccc 1680

tttcacagag tagaacctgg gttagaggat tgcagaagac gagcggcagc ggggagggca 1740

gggaagatgc ctgtcgggtt tttagcacag ttcatttcac tgggattttg aagcatttct 1800

gtctgaatgt aaagcctgtt ctagtcctgg tgggacacac tggggttggg ggtgggggaa 1860

gatgcggtaa tgaaaccggt tagtcagtgt tgtcttaata tccttgataa tgctgtaaag 1920

tttattttta caaatatttc tgtttaagct atttcacctt tgtttggaaa tccttccctt 1980

ttaaagagaa aatgtgacac ttgtgaaaag gcttgtagga aagctcctcc cttttttttct 2040

ttaaaccttt aaatgacaaa cctaggtaat taatggttgt gaatttctat ttttgctttg 2100

tttttaatga acatttgtct ttcagaatag gattctgtga taatatttaa atggcaaaaa 2160

caaaacataa ttttgtgcaa ttaacaaagc tactgcaaga aaaataaaac atttcttggt 2220

aaaaacgtat gtatttatat attatatatt tatatataat atatattata tatttagcat 2280

tgctgagctt tttagatgcc tattgtgtat cttttaaagg ttttgaccat tttgttatga 2340

gtaattacat atatattaca ttcactatat taaaattgta ctttttttact atgtgtctca 2400

ttggttcata gtctttattt tgtcctttga ataaacatta aaagatttct aaacttcaaa 2460

aaaaaaaaaa aaaaa 2475

<210> SEQ ID NO 29
<211> LENGTH: 1677
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

acccсttctt tccacactgc cccctgagtt cagggaattt ccccagcatc ccaaagcttg 60

agtttcctgc cagtcgggag ggatgaatgc agataaaggg agtgcagaag gcacgaggaa 120

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accaaagtgc tctgtatcct ccagtctccg cgcctccacc cagctcagga acccgcgaac    180
cctctcttga ccactatgag cctcccgtcc agccgcgcgg cccgtgtccc gggtccttcg    240
ggctccttgt gcgcgctgct cgcgctgctg ctcctgctga cgccgccggg gcccctcgcc    300
agcgctggtc ctgtctctgc tgtgctgaca gagctgcgtt gcacttgttt acgcgttacg    360
ctgagagtaa accccaaaac gattggtaaa ctgcaggtgt tccccgcagg cccgcagtgc    420
tccaaggtgg aagtggtagc ctccctgaag aacgggaagc aagtttgtct ggacccggaa    480
gccccttttc taaagaaagt catccagaaa attttggaca gtggaaacaa gaaaaactga    540
gtaacaaaaa agaccatgca tcataaaatt gcccagtctt cagcggagca gttttctgga    600
gatccctgga cccagtaaga ataagaagga agggttggtt tttttccatt ttctacatgg    660
attccctact ttgaagagtg tgggggaaag cctacgcttc tccctgaagt ttacagctca    720
gctaatgaag tactaatata gtatttccac tatttactgt tattttacct gataagttat    780
tgaacccttt ggcaattgac catattgtga gcaaagaatc actggttatt agtctttcaa    840
tgaatattga attgaagata actattgtat ttctatcata cattccttaa agtcttaccg    900
aaaaggctgt ggatttcgta tggaaataat gttttattag tgtgctgttg agggaggtat    960
cctgttgttc ttactcactc ttctcataaa ataggaaata ttttagttct gtttcttggg   1020
gaatatgtta ctctttaccc taggatgcta tttaagttgt actgtattag aacactgggt   1080
gtgtcatacc gttatctgtg cagaatatat ttccttattc agaatttcta aaaatttaag   1140
ttctgtaagg gctaatatat tctcttccta tggttttaga cgtttgatgt cttcttagta   1200
tggcataatg tcatgattta ctcattaaac tttgattttg tatgctattt tttcactata   1260
ggatgactat aattctggtc actaaatata cactttagat agatgaagaa gcccaaaaac   1320
agataaattc ctgattgcta atttacatag aaatgtattc tcttggtttt ttaaataaaa   1380
gcaaaattaa caatgatctg tgctctgaaa gttttgaaaa tatatttgaa caatttgaat   1440
ataaattcat catttagtcc tcaaaatata tatagcattg ctaagatttt cagatatcta   1500
ttgtggatct tttaaaggtt ttgaccattt tgttatgagg aattatacat gtatcacatt   1560
cactatatta aaattgcact tttatttttt cctgtgtgtc atgttggttt ttggtacttg   1620
tattgtcatt tggagaaaca ataaaagatt tctaaaccaa aaaaaaaaaa aaaaaaa      1677
```

<210> SEQ ID NO 30
<211> LENGTH: 1307
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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acttatctgc agacttgtag gcagcaactc accctcactc agaggtcttc tggttctgga     60
aacaactcta gctcagcctt ctccaccatg agcctcagac ttgataccac cccttcctgt    120
aacagtgcga gaccacttca tgccttgcag gtgctgctgc ttctgtcatt gctgctgact    180
gctctggctt cctccaccaa aggacaaact aagagaaact tggcgaaagg caaagaggaa    240
agtctagaca gtgacttgta tgctgaactc cgctgcatgt gtataaagac aacctctgga    300
attcatccca aaaacatcca aagtttggaa gtgatcggga aaggaaccca ttgcaaccaa    360
gtcgaagtga tagccacact gaaggatggg aggaaaatct gcctggaccc agatgctccc    420
agaatcaaga aaattgtaca gaaaaaattg gcaggtgatg aatctgctga ttaatttgtt    480
ctgtttctgc caaacttctt taactcccag gaagggtaga attttgaaac cttgattttc    540
```

```
tagagttctc atttattcag gatacctatt cttactgtat taaaatttgg atatgtgttt    600

cattctgtct caaaaatcac attttattct gagaaggttg gttaaaagat ggcagaaaga    660

agatgaaaat aaataagcct ggtttcaacc ctctaattct tgcctaaaca ttggactgta    720

ctttgcattt ttttctttaa aaatttctat tctaacacaa cttggttgat tttttcctggt    780

ctactttatg gttattagac atactcatgg gtattattag atttcataat ggtcaatgat    840

aataggaatt acatggagcc caacagagaa tatttgctca atacattttt gttaatatat    900

ttaggaactt aatggagtct ctcagtgtct tagtcctagg atgtcttatt taaaatactc    960

cctgaaagtt tattctgatg tttattttag ccatcaaaca ctaaaataat aaattggtga   1020

atatgaatct tataaactgt ggttagctgg tttaaagtga atatatttgc cactagtaga   1080

acaaaaatag atgatgaaaa tgaattaaca tatctacata gttataattc tatcattaga   1140

atgagcctta taaataagta caatatagga cttcaacctt actagactcc taattctaaa   1200

ttctactttt ttcatcaaca gaactttcat tcattttta aaccctaaaa cttataccca    1260

cactattctt acaaaaatat tcacatgaaa taaaaatttg ctattga                1307
```

<210> SEQ ID NO 31
<211> LENGTH: 1718
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

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gagggtgcat aagttctcta gtagggtgat gatataaaaa gccaccggag cactccataa     60

ggcacaaact ttcagagaca gcagagcaca caagcttcta ggacaagagc caggaagaaa    120

ccaccggaag gaaccatctc actgtgtgta aacatgactt ccaagctggc cgtggctctc    180

ttggcagcct tcctgatttc tgcagctctg tgtgaaggtg cagttttgcc aaggagtgct    240

aaagaactta gatgtcagtg cataaagaca tactccaaac ctttccaccc caaatttatc    300

aaagaactga gagtgattga gagtggacca cactgcgcca acacagaaat tattgtaaag    360

ctttctgatg gaagagagct ctgtctggac cccaaggaaa actgggtgca gagggttgtg    420

gagaagtttt tgaagagggc tgagaattca taaaaaaatt cattctctgt ggtatccaag    480

aatcagtgaa gatgccagtg aaacttcaag caaatctact tcaacacttc atgtattgtg    540

tgggtctgtt gtagggttgc cagatgcaat acaagattcc tggttaaatt tgaatttcag    600

taaacaatga atagtttttc attgtaccat gaaatatcca gaacatactt atatgtaaag    660

tattatttat ttgaatctac aaaaaacaac aaataatttt taaatataag gattttccta    720

gatattgcac gggagaatat acaaatagca aaattgaggc caagggccaa gagaatatcc    780

gaactttaat ttcaggaatt gaatgggttt gctagaatgt gatatttgaa gcatcacata    840

aaaatgatgg gacaataaat tttgccataa agtcaaattt agctggaaat cctggatttt    900

tttctgttaa atctggcaac cctagtctgc tagccaggat ccacaagtcc ttgttccact    960

gtgccttggt ttctccttta tttctaagtg gaaaaagtat tagccaccat cttacctcac   1020

agtgatgttg tgaggacatg tggaagcact ttaagttttt tcatcataac ataaattatt   1080

ttcaagtgta acttattaac ctatttatta tttatgtatt tatttaagca tcaaatattt   1140

gtgcaagaat ttggaaaaat agaagatgaa tcattgattg aatagttata aagatgttat   1200

agtaaattta ttttatttta gatattaaat gatgttttat tagataaatt tcaatcaggg   1260

tttttagatt aaacaaacaa acaattgggt acccagttaa attttcattt cagataaaca   1320

acaaataatt ttttagtata agtacattat tgtttatctg aaattttaat tgaactaaca   1380
```

atcctagttt gatactccca gtcttgtcat tgccagctgt gttggtagtg ctgtgttgaa 1440

ttacggaata atgagttaga actattaaaa cagccaaaac tccacagtca atattagtaa 1500

tttcttgctg gttgaaactt gtttattatg tacaaataga ttcttataat attatttaaa 1560

tgactgcatt tttaaataca aggctttata tttttaactt taagatgttt ttatgtgctc 1620

tccaaatttt ttttactgtt tctgattgta tggaaatata aaagtaaata tgaaacattt 1680

aaaatataat ttgttgtcaa agtaaaaaaa aaaaaaa 1718

<210> SEQ ID NO 32
<211> LENGTH: 1691
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

aacttcagtt tgttggctgc ggcagcaggt agcaaagtga cgccgagggc ctgagtgctc 60

cagtagccac cgcatctgga gaaccagcgg ttaccatgga ggggatcagt atatacactt 120

cagataacta caccgaggaa atgggctcag gggactatga ctccatgaag gaaccctgtt 180

tccgtgaaga aaatgctaat ttcaataaaa tcttcctgcc caccatctac tccatcatct 240

tcttaactgg cattgtgggc aatggattgg tcatcctggt catgggttac cagaagaaac 300

tgagaagcat gacggacaag tacaggctgc acctgtcagt ggccgacctc ctctttgtca 360

tcacgcttcc cttctgggca gttgatgccg tggcaaactg gtactttggg aacttcctat 420

gcaaggcagt ccatgtcatc tacacagtca acctctacag cagtgtcctc atcctggcct 480

tcatcagtct ggaccgctac ctggccatcg tccacgccac caacagtcag aggccaagga 540

agctgttggc tgaaaaggtg gtctatgttg gcgtctggat ccctgccctc ctgctgacta 600

ttcccgactt catctttgcc aacgtcagtg aggcagatga cagatatatc tgtgaccgct 660

tctaccccaa tgacttgtgg gtggttgtgt tccagtttca gcacatcatg gttggcctta 720

tcctgcctgg tattgtcatc ctgtcctgct attgcattat catctccaag ctgtcacact 780

ccaagggcca ccagaagcgc aaggccctca agaccacagt catcctcatc ctggctttct 840

tcgcctgttg gctgccttac tacattggga tcagcatcga ctccttcatc ctcctggaaa 900

tcatcaagca agggtgtgag tttgagaaca ctgtgcacaa gtggatttcc atcaccgagg 960

ccctagcttt cttccactgt tgtctgaacc ccatcctcta tgctttcctt ggagccaaat 1020

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aagttacaca tttttcagat ataaaagact gaccaatatt gtacagtttt tattgcttgt 1260

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ggaacgtttt tcctgttctt aagacgtgat tttgctgtag aagatggcac ttataaccaa 1560

agcccaaagt ggtatagaaa tgctggtttt tcagttttca ggagtgggtt gatttcagca 1620

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aaaaaaaaaa a 1691

<210> SEQ ID NO 33
<211> LENGTH: 3545
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

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aagtaggaag taaattatag tgatgtaatc ttgaattgta actgttcttg aatttaataa 2040

tctgtagggt aattagtaac atgtgttaag tattttcata agtatttcaa attggagctt 2100

catggcagaa ggcaaaccca tcaacaaaaa ttgtccctta aacaaaaatt aaaatcctca 2160

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<210> SEQ ID NO 34
<211> LENGTH: 2896
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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aaacctccaa gagagctagg gttcctctca gagaggaaag acaggtcctt aggtcctcac    180
cctcccgtct ccttgccctt gcagttctgg gaactggaca gattggacaa ctataacgac    240
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gagggctctg tgggctgggt cctggggacc ttcctctgca aaactgtgat tgccctgcac    540
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gccattgtcc acgccgtcca tgcctaccgc caccgccgcc tcctctccat ccacatcacc    660
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<210> SEQ ID NO 35
<211> LENGTH: 2919

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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gggagcctct caacataaga cagtgaccag tctggtgact cacagccggc acagccatga    180
actacccgct aacgctggaa atggacctcg agaacctgga ggacctgttc tgggaactgg    240
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<210> SEQ ID NO 36
<211> LENGTH: 1219
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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agcagcctct ctccagtcca aggtgttctg gaggtctatt acacaagctt gaggtgtaga 180

tgtgtccaag agagctcagt ctttatccct agacgcttca ttgatcgaat tcaaatcttg 240

ccccgtggga atggttgtcc aagaaaagaa atcatagtct ggaagaagaa caagtcaatt 300

gtgtgtgtgg accctcaagc tgaatggata caaagaatga tggaagtatt gagaaaaaga 360

agttcttcaa ctctaccagt tccagtgttt aagagaaaga ttccctgatg ctgatatttc 420

cactaagaac acctgcattc ttcccttatc cctgctctgg attttagttt tgtgcttagt 480

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gaaaacaatg gaatgagaat ttaagcctca aatttgaaca tgtggcttga attaagaaga 780

aaattatggc atatattaaa agcaggcttc tatgaaagac tcaaaaagct gcctgggagg 840

cagatggaac ttgagcctgt caagaggcaa aggaatccat gtagtagata tcctctgctt 900

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tcacatcttt ttcactgact ttttttgtgg ggggcggggc cggggggact ctggtatcta 1140

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taaaaaaaaa aaaaaaaaa 1219

<210> SEQ ID NO 37
<211> LENGTH: 1953
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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<210> SEQ ID NO 38
<211> LENGTH: 2344
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

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ccaccgggcc gcccgggagg ctcatgcagc gcggctgggt cccgcggcgc ccggatcggg    120
gaagtgaaag tgcctcggag gaggagggcc ggtccggcag tgcagccgcc tcacaggtcg    180
gcggacgggc caggcgggcg gcctcctgaa ccgaaccgaa tcggctcctc gggccgtcgt    240
cctcccgccc ctcctcgccc gccgccggag ttttctttcg gtttcttcca agattcctgg    300
ccttccctcg acggagccgg gcccagtgcg ggggcgcagg gcgcgggagc tccacctcct    360
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ggcacagcag ggccgggggg tgcagctggc tcgcgcctcc tctccggccg ccgtctcctc    480
cggtccccgg cgaaagccat tgagacacca gctggacgtc acgcgccgga gcatgtctgg    540
gagtcagagc gaggtggctc catccccgca gagtccgcgg agccccgaga tgggacggga    600
cttgcggccc gggtcccgcg tgctcctgct cctgcttctg ctcctgctgg tgtacctgac    660
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caacaaggac ccatgggttc aggaattgat gagctgtctt gatctcaaag aatgtggaca    900
tgcttactcg ggattgtgg cccaccagaa gcatttactt cctaccagcc ccccaatttc    960
tcaggcctca gagggggcat cttcagatat ccacacccct gcccagatgc tcctgtccac   1020
cttgcagtcc actcagcgcc ccaccctccc agtaggatca ctgtcctcgg acaaagagct   1080
cactcgtccc aatgaaacca ccattcacac tgcgggccac agtctggcag ctgggcctga   1140
ggctggggag aaccagaagc agccggaaaa aaatgctggt cccacagcca ggacatcagc   1200
cacagtgcca gtcctgtgcc tcctggccat catcttcatc ctcaccgcag ccctttccta   1260
tgtgctgtgc aagaggagga gggggcagtc accgcagtcc tctccagatc tgccggttca   1320
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cggactctat gttgcccagg ctgttatgga actcctgagt caagtgatcc tcccaccttg   1440
gcctctgaag gtgcgaggat tataggcgtc acctaccaca tccagcctac acgtatttgt   1500
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gttatactat aaaatctgct tttcacactg ggtgataata acttggacaa attctatgtg   1620
tattttgttt tgttttgctt tgctttgttt tgagacggag tctcgctctg tcatccaggc   1680
tggagtgcag tggcatgatc tcggctcact gcaaccccca tctcccaggt tcaagcgatt   1740
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tttgtatttt tagtagagac ggggtttcac catgttgacc aggctggtct cgaactcctg   1860
acctggtgat ctgcccaccc aggcctccca aagtgctggg attaaaggtg tgagccacca   1920
tgcctggccc tatgtgtgtt ttttaactac taaaaattat ttttgtaatg attgagtctt   1980
ctttatggaa acaactggcc tcagcccttg cgcccttact gtgattcctg gcttcatttt   2040
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acctcagccc tctcctgcat cctcctgtac ccgcaacgaa ggcctgggct ttcccaccct   2160
ccctccttag caggtgccgt gctgggacac catacgggtt ggtttcacct cctcagtccc   2220
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<210> SEQ ID NO 39
<211> LENGTH: 1497
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

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tgagaggatg aaggtctccg aggctgccct gtctctcctt gtcctcatcc ttatcattac 120

ttcggcttct cgcagccagc caaaagttcc tgagtgggtg aacaccccat ccacctgctg 180

cctgaagtat tatgagaaag tgttgccaag gagactagtg gtgggataca gaaaggccct 240

caactgtcac ctgccagcaa tcatcttcgt caccaagagg aaccgagaag tctgcaccaa 300

ccccaatgac gactgggtcc aagagtacat caaggatccc aacctacctt tgctgcctac 360

caggaacttg tccacggtta aaattattac agcaaagaat ggtcaacccc agctcctcaa 420

ctcccagtga tgaccaggct ttagtggaag cccttgttta cagaagagag ggtaaacct 480

atgaaaacag gggaagcctt attaggctga aactagccag tcacattgag agaagcagaa 540

caatgatcaa aataaaggag aagtatttcg aatattttct caatcttagg aggaaatacc 600

aaagttaagg gacgtgggca gaggtacgct cttttatttt tatatttata tttttatttt 660

tttgagatag ggtcttactc tgtcacccag gctggagtgc agtggtgtga tcttggctca 720

cttgatcttg gctcactgta acctccacct cccaggctca agtgatcctc ccaccccagc 780

ctcctgagta gctgggacta caggcttgcg ccaccacacc tggctaattt ttgtattttt 840

ggtagagacg ggattctacc atgttgccca ggctggtctc aaactcgtgt gcccaagcaa 900

tccacctgcc tcagccttcc aaaagtgctg ggattacagg cgtgagccac cacatccggc 960

cagtgcactc ttaatacaca gaaaaatata tttcacatcc ttctcctgct ctctttcaat 1020

tcctcacttc acaccagtac acaagccatt ctaaatactt agccagtttc cagccttcca 1080

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ctgtccatct ttatggattt ttctggatct atattttctt caattattct ttcattttat 1200

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actttgctag atcctctcat attttgtctt cctcagggtg gcaggggtac agagagtgcc 1320

tgattggaaa aaaaaaaaaa agagagagag agagaagaag aagaagaaga gacacaaatc 1380

tctacctccc atgttaagct ttgcaggaca gggaaagaaa gggtatgaga cacggctagg 1440

ggtaaactct tagtccaaaa cccaagcatg caataaataa aactccctta tttgaca 1497

<210> SEQ ID NO 40
<211> LENGTH: 1002
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

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tggctcctgg cctgcctggt ggccggcttc ctgggagcct gggcccccgc tgtccacacc 180

caaggtgtct ttgaggactg ctgcctggcc taccactacc ccattgggtg ggctgtgctc 240

cggcgcgcct ggacttaccg gatccaggag gtgagcggga gctgcaatct gcctgctgcg 300

atattctacc tccccaagag acacaggaag gtgtgtggga accccaaaag cagggaggtg 360

cagagagcca tgaagctcct ggatgctcga aataaggttt ttgcaaagct ccaccacaac 420

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acgcagacct tccaagcagg ccctcatgct gtaaagaagt tgagttctgg aaactccaag    480
ttatcatcgt ccaagtttag caatcccatc agcagcagta agaggaatgt ctccctcctg    540
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gccggatctt tctccgataa aaccgtcgcc ctacagaccc agctgtcccc acgcctctgt    660
cttttgggtc aagtcttaat ccctgcacct gagttggtcc tccctctgca cccccaccac    720
ctcctgcccg tctggcaact ggaaagaggg agttggcctg attttaagcc ttttgccgct    780
ccggggacca gcagcaatcc tgggcagcca gtggctcttg tagagaagac ttaggatacc    840
tctctcactt tctgtttctt gccgtccacc ccgggccatg ccagtgtgtc cctctgggtc    900
cctccaaaac tctggtcagt tcaaggatgc ccctcccagg ctatgctttt ctataacttt    960
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<210> SEQ ID NO 41
<211> LENGTH: 1002
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

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tggctcctgg cctgcctggt ggccggcttc ctgggagcct gggcccccgc tgtccacacc    180
caaggtgtct ttgaggactg ctgcctggcc taccactacc ccattgggtg ggctgtgctc    240
cggcgcgcct ggacttaccg gatccaggag gtgagcggga gctgcaatct gcctgctgcg    300
atattctacc tccccaagag acacaggaag gtgtgtggga accccaaaag cagggaggtg    360
cagagagcca tgaagctcct ggatgctcga aataaggttt ttgcaaagct ccaccacaac    420
acgcagacct tccaagcagg ccctcatgct gtaaagaagt tgagttctgg aaactccaag    480
ttatcatcgt ccaagtttag caatcccatc agcagcagta agaggaatgt ctccctcctg    540
atatcagcta attcaggact gtgagccggc tcatttctgg gctccatcgg cacaggaggg    600
gccggatctt tctccgataa aaccgtcgcc ctacagaccc agctgtcccc acgcctctgt    660
cttttgggtc aagtcttaat ccctgcacct gagttggtcc tccctctgca cccccaccac    720
ctcctgcccg tctggcaact ggaaagaggg agttggcctg attttaagcc ttttgccgct    780
ccggggacca gcagcaatcc tgggcagcca gtggctcttg tagagaagac ttaggatacc    840
tctctcactt tctgtttctt gccgtccacc ccgggccatg ccagtgtgtc cctctgggtc    900
cctccaaaac tctggtcagt tcaaggatgc ccctcccagg ctatgctttt ctataacttt    960
taaataaacc ttgggggtg atggagtcat tcctgcctgt ta                       1002

<210> SEQ ID NO 42
<211> LENGTH: 744
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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gtccacaccc aaggtgtctt tgaggactgc tgcctggcct accactaccc cattgggtgg    120
gctgtgctcc ggcgcgcctg gacttaccgg atccaggagg tgagcgggag ctgcaatctg    180
cctgctgcga tcaggccctc atgctgtaaa gaagttgagt tctggaaact ccaagttatc    240
atcgtccaag tttagcaatc ccatcagcag cagtaagagg aatgtctccc tcctgatatc    300
```

```
agctaattca ggactgtgag ccggctcatt tctgggctcc atcggcacag gaggggccgg    360

atctttctcc gataaaaccg tcgccctaca gacccagctg tccccacgcc tctgtctttt    420

gggtcaagtc ttaatccctg cacctgagtt ggtcctccct ctgcaccccc accacctcct    480

gcccgtctgg caactggaaa gagggagttg gcctgatttt aagccttttg ccgctccggg    540

gaccagcagc aatcctgggc agccagtggc tcttgtagag aagacttagg atacctctct    600

cactttctgt ttcttgccgt ccaccccggg ccatgccagt gtgtccctct gggtccctcc    660

aaaactctgg tcagttcaag gatgcccctc ccaggctatg cttttctata acttttaaat    720

aaaccttggg gggtgatgga gtca                                           744
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<210> SEQ ID NO 43
<211> LENGTH: 3108
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

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aaaactttga gtacgatgat ttggctgagg cctgttatat tggggacatc gtggtctttg    180

ggactgtgtt cctgtccata ttctactccg tcatctttgc cattggcctg gtgggaaatt    240

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tcatcggctt ttttggaagc atattcttca tcaccgtcat cagcattgat aggtacctgg    480

ccatcgtcct ggccgccaac tccatgaaca accggaccgt gcagcatggc gtcaccatca    540

gcctaggcgt ctgggcagca gccattttgg tggcagcacc ccagttcatg ttcacaaagc    600

agaaagaaaa tgaatgcctt ggtgactacc ccgaggtcct ccaggaaatc tggcccgtgc    660

tccgcaatgt ggaaacaaat tttcttggct tcctactccc cctgctcatt atgagttatt    720

gctacttcag aatcatccag acgctgtttt cctgcaagaa ccacaagaaa gccaaagcca    780

ttaaactgat ccttctggtg gtcatcgtgt ttttcctctt ctggacaccc tacaacgtta    840

tgattttcct ggagacgctt aagctctatg acttctttcc cagttgtgac atgaggaagg    900

atctgaggct ggccctcagt gtgactgaga cggttgcatt tagccattgt tgcctgaatc    960

ctctcatcta tgcatttgct ggggagaagt tcagaagata cctttaccac ctgtatggga   1020

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atgcattgct ccttctctga agggaatccc aaagccttgt gtctacagag aacctggagt   1200

tcctgaacct gatgctgact agtgaggaaa gatttttgtt gttatttctt acaggcacaa   1260

aatgatggac ccaatgcaca caaaacaacc ctagagtgtt gttgagaatt gtgctcaaaa   1320

tttgaagaat gaacaaattg aactctttga atgacaaaga gtagacattt ctcttactgc   1380

aaatgtcatc agaacttttt ggtttgcaga tgacaaaaat tcaactcaga ctagtttagt   1440

taaatgaggg tggtgaatat tgttcatatt gtggcacaag caaaagggtg tctgagccct   1500

caaagtgagg ggaaaccagg gcctgagcca agctagaatt ccctctctct gactctcaaa   1560

tcttttagtc attatagatc ccccagactt tacatgacac agctttatca ccagagaggg   1620
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actgacaccc atgtttctct ggccccaagg gcaaaattcc cagggaagtg ctctgatagg 1680
ccaagtttgt atcaggtgcc catccctgga aggtgctgtt atccatgggg aagggatata 1740
taagatggaa gcttccagtc caatctcatg gagaagcaga aatacatatt tccaagaagt 1800
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tgcctgatcc agcctctccc ctgattacac cagcctcgtc ttcattaagc cctcttccat 1920
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gtttggaaca atctaaaagt ttaaagctcg aaaacaattg taataatgct aaagaaaaag 2700
tcatccaatc taaccacatc aatattgtca ttcctgtatt cacccgtcca gaccttgttc 2760
acactctcac atgtttagag ttgcaatcgt aatgtacaga tggttttata atctgatttg 2820
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<210> SEQ ID NO 44
<211> LENGTH: 3304
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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gactgtcctg ctggctggac agcaccacgg tgtgacgaaa tgcaacatca cgtgcagcaa 180
gatgacatca aagatacctg tagctttgct catccactat caacagaacc aggcatcatg 240
cggcaaacgc gcaatcatct tggagacgag acagcacagg ctgttctgtg ccgacccgaa 300
ggagcaatgg gtcaaggacg cgatgcagca tctggaccgc caggctgctg ccctaactcg 360
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cgggggaatg gacgagtctg tggtcctgga gcccgaagcc acaggcgaaa gcagtagcct 480
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gacgggcgtg actggttcct cagggaccag gctccccccg acgccaaagg ctcaggatgg 600
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gagttctgct ccccaccaac ctgggcccag cctctgggct gaggcaaaga cctctgaggc    720
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gaatgctccg tctgaaggcc agcgtgtgtg gggtcaggga cagagcccca ggccagagaa    840
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ggggcctggc agcatggccc acgtctctgt ggtccctgtc tcctcagaag ggacccccag    960
cagggagcca gtggcttcag gcagctggac ccctaaggct gaggaaccca tccatgccac   1020
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aactcctctg gcctgtgtct agttgtttga ttcagacagc tgcctgggat ccctcatcct   1320
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gctgccctgc ccacctggcc tctgcactcc cctgctgggt gtggcgcagc atattcagga   2940
agctcagggc ctggctcagg tggggtcact ctggcagctc agagagggtg ggagtgggtc   3000
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caatgcactt tgttctggct cttccaggct gggagagcct ttcaggggtg ggacaccctg 3060

tgatggggcc ctgcctcctt tgtgaggaag ccgctggggc cagttggtcc cccttccatg 3120

gactttgtta gtttctccaa gcaggacatg gacaaggatg atctaggaag actttggaaa 3180

gagtaggaag actttggaaa gacttttcca accctcatca ccaacgtctg tgccattttg 3240

tattttacta ataaaattta aaagtcttgt gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3300

aaaa 3304

<210> SEQ ID NO 45
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Arg Ser Ser Ser Thr Leu Pro Val Pro Val Phe Lys Arg Lys Ile Pro
1 5 10 15

<210> SEQ ID NO 46
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp Lys Lys
1 5 10 15

<210> SEQ ID NO 47
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp Lys
1 5 10 15

<210> SEQ ID NO 48
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val
1 5 10 15

<210> SEQ ID NO 49
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp
1 5 10 15

<210> SEQ ID NO 50
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile
1 5 10 15

<210> SEQ ID NO 51
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp Lys Lys Asn
1 5 10 15

<210> SEQ ID NO 52
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Lys Arg Ser Ser Ser Thr Leu Pro Val Pro Val Phe Lys Arg Lys Ile
1 5 10 15

<210> SEQ ID NO 53
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile
1 5 10 15

<210> SEQ ID NO 54
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys Glu
1 5 10 15

<210> SEQ ID NO 55
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Arg Lys Arg Ser Ser Ser Thr Leu Pro Val Pro Val Phe Lys Arg Lys
1 5 10 15

<210> SEQ ID NO 56
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Arg Cys Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe
1 5 10 15

<210> SEQ ID NO 57
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Gly Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp Lys Lys Asn Lys
1 5 10 15

<210> SEQ ID NO 58
<211> LENGTH: 16

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile Asp Arg
1 5 10 15

<210> SEQ ID NO 59
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Ile Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg Lys
1 5 10 15

<210> SEQ ID NO 60
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Leu Arg Cys Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg
1 5 10 15

<210> SEQ ID NO 61
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Phe Ile Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro Arg
1 5 10 15

<210> SEQ ID NO 62
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile Asp
1 5 10 15

<210> SEQ ID NO 63
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Cys Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile
1 5 10 15

<210> SEQ ID NO 64
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile Asp Arg Ile Gln
1 5 10 15

<210> SEQ ID NO 65
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Arg Phe Ile Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys Pro
1 5 10 15

<210> SEQ ID NO 66
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile Asp Arg Ile
1 5 10 15

<210> SEQ ID NO 67
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Glu Ser Ser Val Phe Ile Pro Arg Arg Phe Ile Asp Arg Ile Gln Ile
1 5 10 15

<210> SEQ ID NO 68
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Ser Leu Arg Cys Arg Cys Val Gln Glu Ser Ser Val Phe Ile Pro Arg
1 5 10 15

<210> SEQ ID NO 69
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Asn Gly Cys Pro Arg Lys Glu Ile Ile Val Trp Lys Lys Asn Lys Ser
1 5 10 15

<210> SEQ ID NO 70
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Pro Gln Ala Glu Trp Ile Gln Arg Met Met Glu Val Leu Arg Lys Arg
1 5 10 15

<210> SEQ ID NO 71
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Arg Arg Phe Ile Asp Arg Ile Gln Ile Leu Pro Arg Gly Asn Gly Cys
1 5 10 15

<210> SEQ ID NO 72
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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Leu Arg Lys Arg Ser Ser Ser Thr Leu Pro Val Pro Val Phe Lys Arg
1               5                   10                  15


<210> SEQ ID NO 73
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Val Gln Glu Ser Ser Val Phe Ile Pro Arg Arg
1               5                   10


<210> SEQ ID NO 74
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Glu Trp Ile Gln Arg Met Met Glu Val Leu Arg Lys Arg Ser Ser Ser
1               5                   10                  15

Thr Leu Pro Val Pro Val Phe Lys Arg Lys
            20                  25


<210> SEQ ID NO 75
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Lys Lys Asn Lys
1


<210> SEQ ID NO 76
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Arg Lys Arg Ser Ser Ser
1               5


<210> SEQ ID NO 77
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Arg Gly Asn Gly Cys Pro
1               5


<210> SEQ ID NO 78
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Val Tyr Tyr Thr Ser Leu Arg Cys Arg Cys Val Gln Glu Ser Ser Val
1               5                   10                  15

Phe Ile Pro Arg Arg
            20


<210> SEQ ID NO 79
<211> LENGTH: 7
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Asp Arg Ile Gln Ile Leu Pro
1   5

<210> SEQ ID NO 80
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Arg Lys Glu Ile Ile Val Trp
1   5

<210> SEQ ID NO 81
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Lys Ser Ile Val Cys Val Asp Pro Gln
1   5

<210> SEQ ID NO 82
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Thr Ser Leu Val Glu Asn His Leu Cys Pro Ala Thr Glu
1   5   10

<210> SEQ ID NO 83
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Glu Gly Ser Val Gly Trp Val Leu Gly Thr Phe Leu Cys Lys Thr
1   5   10   15

<210> SEQ ID NO 84
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Leu Pro Arg Cys Thr Phe Ser
1   5

<210> SEQ ID NO 85
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Leu Ala Arg Leu Lys Ala Val Asp Asn Thr
1   5   10

<210> SEQ ID NO 86
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Met Ala Ser Phe Lys Ala Val Phe Val Pro
1 5 10

<210> SEQ ID NO 87
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Ala Ala Gly Pro Glu Ala Gly Glu Asn Gln Lys Gln Pro Glu Lys Asn
1 5 10 15

<210> SEQ ID NO 88
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Ser Gln Ala Ser Glu Gly Ala Ser Ser Asp Ile His Thr Pro Ala Gln
1 5 10 15

<210> SEQ ID NO 89
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

Ser Thr Leu Gln Ser Thr Gln Arg Pro Thr Leu Pro Val Gly Ser Leu
1 5 10 15

<210> SEQ ID NO 90
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Ser Trp Ser Val Cys Gly Gly Asn Lys Asp Pro Trp Val Gln Glu Leu
1 5 10 15

<210> SEQ ID NO 91
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Gly Pro Thr Ala Arg Thr Ser Ala Thr Val Pro Val Leu Cys Leu Leu
1 5 10 15

<210> SEQ ID NO 92
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Ser Gly Ile Val Ala His Gln Lys His Leu Leu Pro Thr Ser Pro Pro
1 5 10 15

<210> SEQ ID NO 93
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

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Arg Leu Arg Lys His Leu
1               5


<210> SEQ ID NO 94
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Leu Gln Ser Thr Gln Arg Pro
1               5


<210> SEQ ID NO 95
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Ser Ser Asp Lys Glu Leu Thr Arg Pro Asn Glu Thr Thr
1               5                   10


<210> SEQ ID NO 96
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Ala Gly Glu Asn Gln Lys Gln Pro Glu Lys Asn Ala
1               5                   10


<210> SEQ ID NO 97
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Asn Glu Gly Ser Val Thr
1               5


<210> SEQ ID NO 98
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Ile Ser Ser Asp Ser Pro Pro Ser Val
1               5


<210> SEQ ID NO 99
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Cys Gly Gly Asn Lys Asp Pro Trp
1               5


<210> SEQ ID NO 100
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Leu Leu Pro Thr Ser Pro Pro Ile Ser Gln Ala Ser Glu Gly Ala Ser
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1               5                   10                  15

Ser Asp Ile His Thr
            20


<210> SEQ ID NO 101
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Ser Thr Gln Arg Pro Thr Leu Pro Val Gly Ser Leu Ser Ser Asp Lys
1               5                   10                  15

Glu Leu Thr Arg Pro Asn Glu Thr Thr Ile His Thr
            20                  25


<210> SEQ ID NO 102
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Ser Leu Ala Ala Gly Pro Glu Ala Gly Glu Asn Gln Lys Gln Pro Glu
1               5                   10                  15

Lys Asn Ala Gly Pro Thr Ala Arg Thr Ser Ala
            20                  25


<210> SEQ ID NO 103
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Thr Gly Ser Cys Tyr Cys Gly Lys Arg
1               5


<210> SEQ ID NO 104
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Asp Ser Pro Pro Ser Val Gln
1               5


<210> SEQ ID NO 105
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Arg Lys His Leu Arg Ala Tyr His Arg Cys Leu Tyr Tyr Thr Arg Phe
1               5                   10                  15

Gln Leu Leu Ser Trp Ser Val Cys Gly Gly
            20                  25


<210> SEQ ID NO 106
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Trp Val Gln Glu Leu Met Ser Cys Leu Asp Leu Lys Glu Cys Gly His
1               5                   10                  15
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Ala Tyr Ser Gly Ile Val Ala His Gln Lys His Leu Leu Pro Thr Ser
            20                  25                  30

Pro Pro Ile Ser Gln
        35


<210> SEQ ID NO 107
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Ser Asp Ile His Thr Pro Ala Gln Met Leu Leu Ser Thr Leu Gln
1               5                   10                  15


<210> SEQ ID NO 108
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Arg Pro Thr Leu Pro Val Gly Ser Leu
1               5


<210> SEQ ID NO 109
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Thr Ala Gly His Ser Leu Ala Ala Gly
1               5


<210> SEQ ID NO 110
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Gly Lys Arg Ile Ser Ser Asp Ser Pro Pro Ser Val Gln
1               5                   10


<210> SEQ ID NO 111
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Lys Asp Pro Trp Val Gln Glu Leu Met Ser Cys Leu Asp Leu Lys Glu
1               5                   10                  15

Cys Gly His Ala Tyr Ser Gly Ile Val Ala His Gln Lys His
            20                  25                  30


<210> SEQ ID NO 112
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

His Gln Asp Phe Leu Gln Phe Ser Lys Val
1               5                   10


<210> SEQ ID NO 113
<211> LENGTH: 14
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Ala Gly Ile His Glu Trp Val Phe Gly Gln Val Met Cys Lys
1   5   10

<210> SEQ ID NO 114
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Pro Gln Ile Ile Tyr Gly Asn Val Phe Asn Leu Asp Lys Leu Ile Cys
1   5   10   15

Gly Tyr His Asp Glu Ala Ile
            20

<210> SEQ ID NO 115
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Tyr Tyr Ala Met Thr Ser Phe His Tyr Thr Ile Met Val Thr Glu Ala
1   5   10   15

<210> SEQ ID NO 116
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Leu Ala Tyr His Tyr Pro Ile Gly Trp Ala Val Leu
1   5   10

<210> SEQ ID NO 117
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys Ser Arg Glu Val Gln
1   5   10   15

Arg Ala Met Lys Leu Leu Asp Ala Arg Asn Lys Val Phe Ala Lys Leu
            20   25   30

His His

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Phe Glu Asp Cys Cys Leu Ala Tyr His Tyr Pro Ile Gly Trp Ala Val
1   5   10   15

Leu Arg Arg Ala
            20

<210> SEQ ID NO 119
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Ile Gln Glu Val Ser Gly Ser Cys Asn Leu Pro Ala Ala Ile Phe Tyr
1 5 10 15

Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn
20 25

<210> SEQ ID NO 120
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Ala Met Lys Leu Leu Asp Ala Arg
1 5

<210> SEQ ID NO 121
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Lys Val Phe Ala Lys Leu His His Asn
1 5

<210> SEQ ID NO 122
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Gln Ala Gly Pro His Ala Val Lys Lys Leu
1 5 10

<210> SEQ ID NO 123
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Phe Tyr Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro
1 5 10

<210> SEQ ID NO 124
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Tyr Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Leu Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys Ser
1 5 10

<210> SEQ ID NO 126
<211> LENGTH: 14
<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Pro Lys Arg His Arg Lys Val Cys Gly Asn Pro Lys Ser Arg
1   5   10

<210> SEQ ID NO 127
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Cys Gly Asn Pro Lys Ser Arg Glu Val Gln Arg Ala Met Lys
1   5   10

<210> SEQ ID NO 128
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Gly Asn Pro Lys Ser Arg Glu Val Gln Arg Ala Met Lys Leu
1   5   10

<210> SEQ ID NO 129
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Lys Phe Ser Asn Pro Ile Ser Ser Ser Lys Arg Asn Val Ser
1   5   10

<210> SEQ ID NO 130
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Pro Lys Ser Arg Glu Val
1   5

<210> SEQ ID NO 131
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Leu His His Asn Thr Gln Thr
1   5

<210> SEQ ID NO 132
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Ser Ser Ser Lys Arg Asn
1   5

<210> SEQ ID NO 133
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 133

Gln Phe Ala Ser His Phe Leu Pro Pro
1               5


<210> SEQ ID NO 134
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Ala Ala Ala Asp Gln Trp Lys Phe Gln
1               5


<210> SEQ ID NO 135
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Thr Phe Met Cys Lys Val Val Asn Ser Met
1               5                   10


<210> SEQ ID NO 136
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Ile Ala Ile Cys Thr Met Val Tyr Pro Ser
1               5                   10


<210> SEQ ID NO 137
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Val Gln Thr Ile Asp Ala Tyr Ala Met Phe Ile Ser Asn Cys Ala Val
1               5                   10                  15

Ser Thr Asn Ile Asp Ile Cys Phe Gln
            20                  25
```

What is claimed is:

1. A method for prevention or inhibition of the migration or metastasis of carcinoma cells with elevated expression of CCL25 in a subject, comprising:

measuring expression of CCL25 in a sample of metastasizing carcinoma cells extracted from the subject;

determining overexpression of CCL25 in the sample of metastasizing cancer cells;

administering to the subject with metastasizing carcinoma cells having overexpression of CCL25 a therapeutically effective amount of an anti-CCL25 antibody, wherein said therapeutically effective amount is between about 0.5 and 50 mg/kg.

2. The method of claim **1**, wherein said anti-CCL25 antibody is administered directly into a carcinoma tissue.

3. The method of claim **1**, wherein said anti-CCL25 antibody is administered in conjunction with a chemotherapeutic agent.

4. The method of claim **1**, wherein said anti-CCL25 antibody is administered in conjunction with another anti-chemokine or anti-chemokine receptor antibody selected from the group consisting of CCL1, CCL4, CCL17, CCL19, CCL21, CCL22, CXCL12, CXCL13, CXCL16, CCR7, CCR8, CCR9, CXCR4, CXCR5, CXCR6 and CX3CR1.

5. The method of claim **1**, wherein the subject is further administered a therapeutically effective amount of an anti-CCR9 antibody.

6. A method for enhancing the effect of chemotherapy, comprising:

measuring expression of CCL25 in a sample of metastasizing carcinoma cells extracted from a subject who is under chemotherapy for a metastasizing cancer;

determining overexpression of CCL25 in the sample of metastasizing carcinoma cancer cells;

administering to the subject who has overexpression of CCL25 in the sample of metastasizing carcinoma cells an effective amount of an anti-CCL25 antibody, wherein said effective amount is between about 0.5 and 50 mg/kg.

* * * * *